III sessione:

VIVERE CON IL CARCINOMA MAMMARIO METASTATICO:

Nuove opzioni terapeutiche nel carcinoma mammario metastatico nel 2023.

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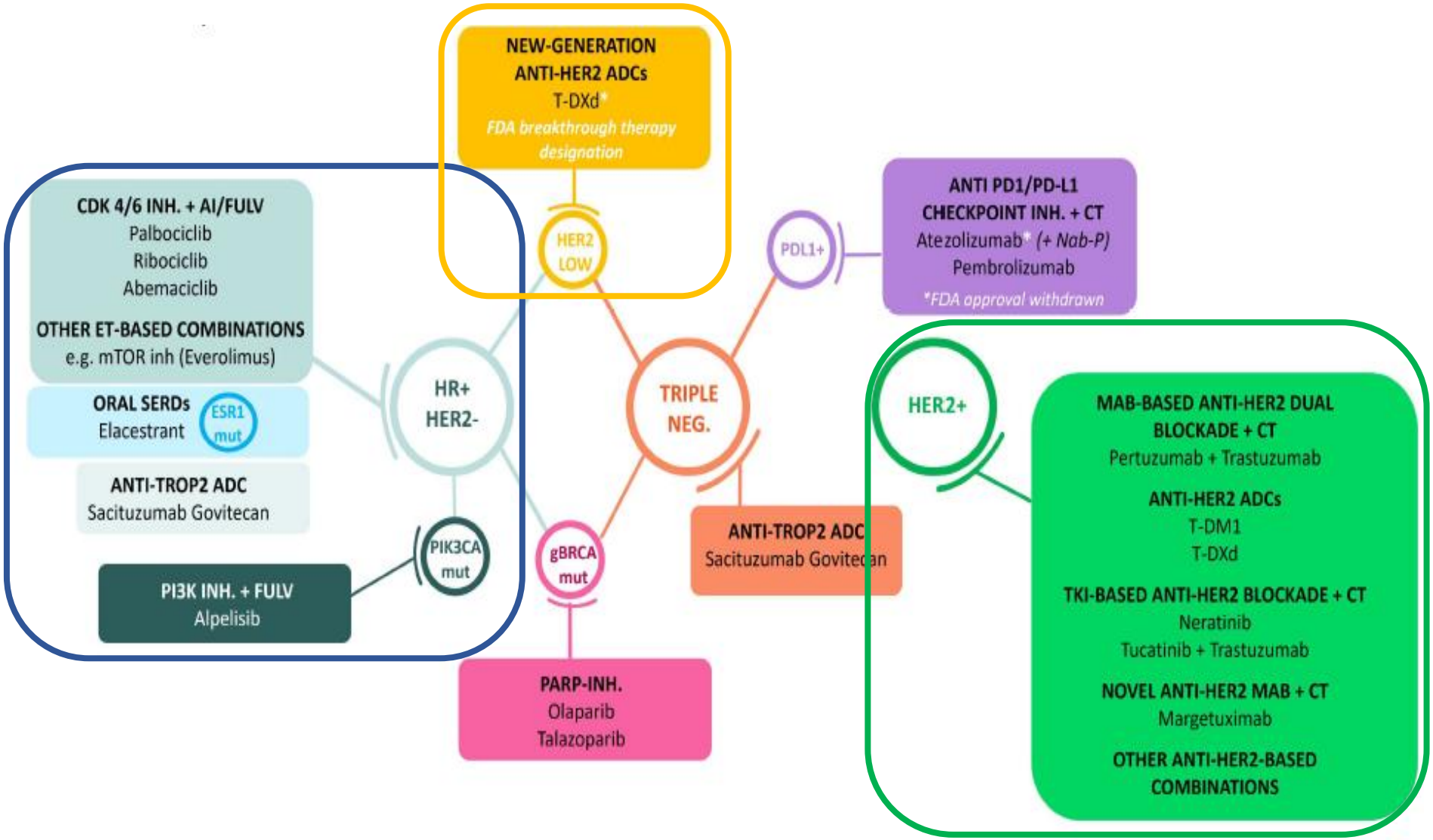
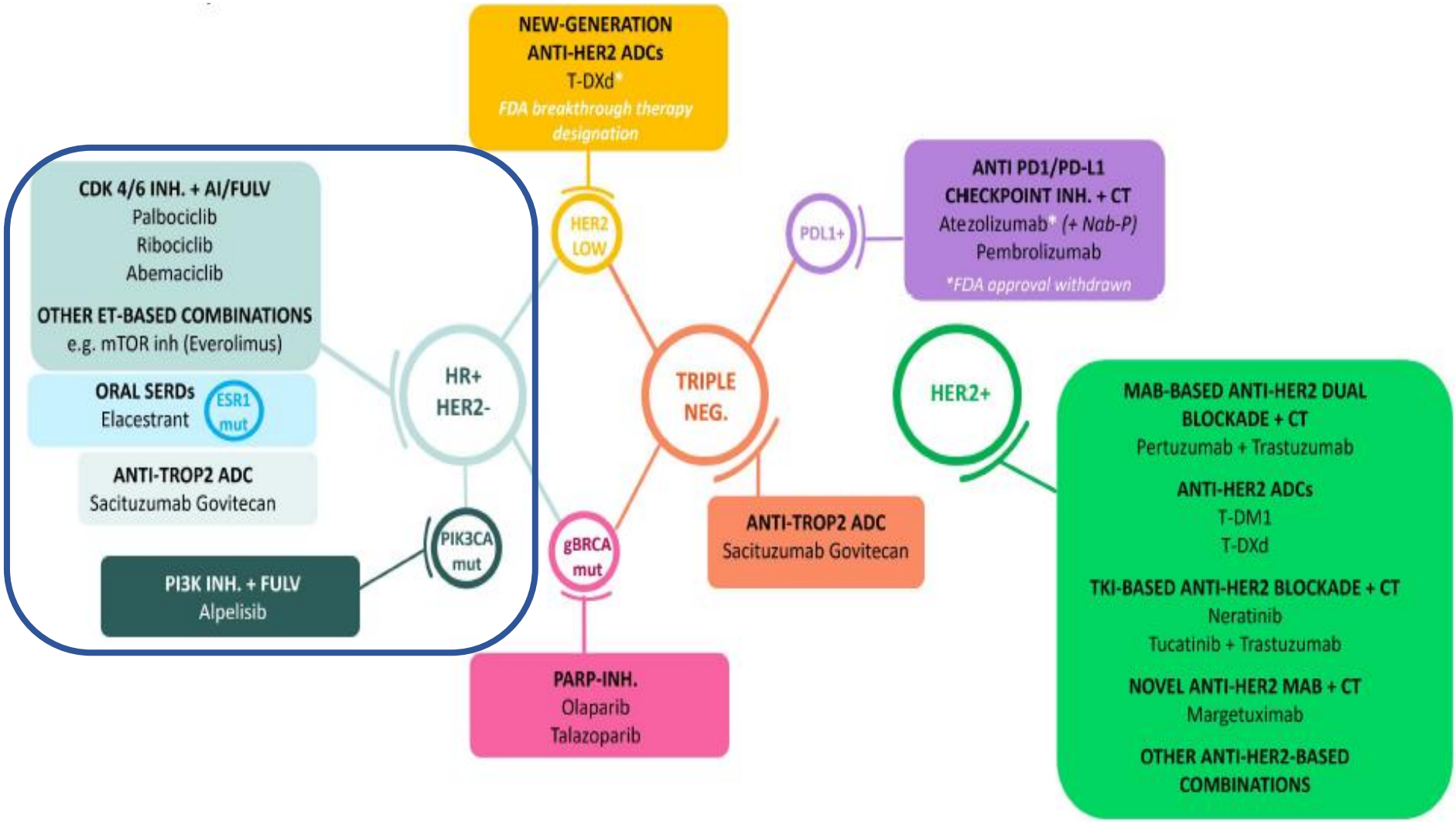
Oncologia Medica - Direttore: Dott. Stefania Gori
IRCCS Ospedale «Sacro Cuore - Don Calabria»,
Negrar di Valpolicella (VR)

Breast cancer subgroups:



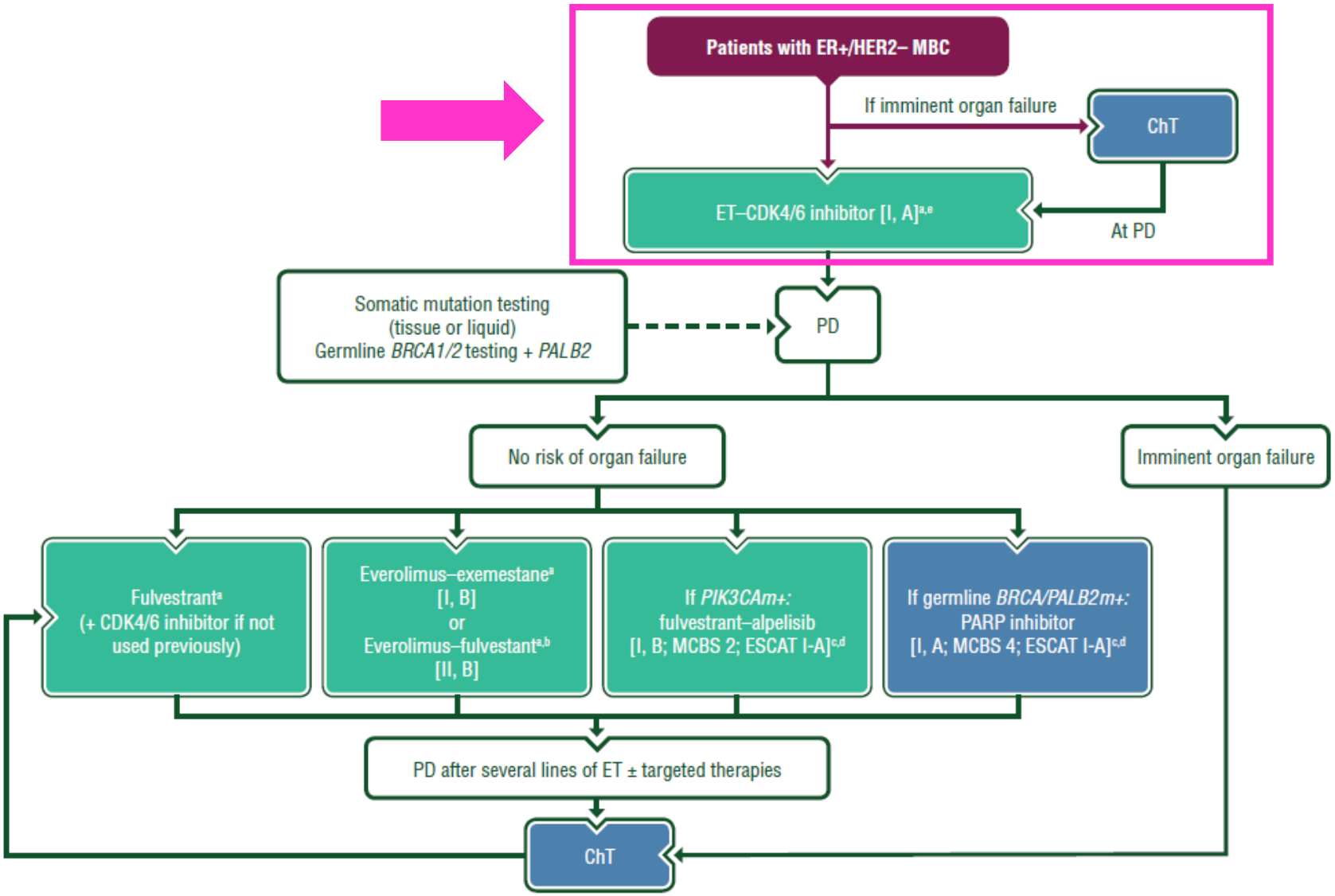
Miglietta F et al., ESMO Open 2022

HR+/HER2- MBC:



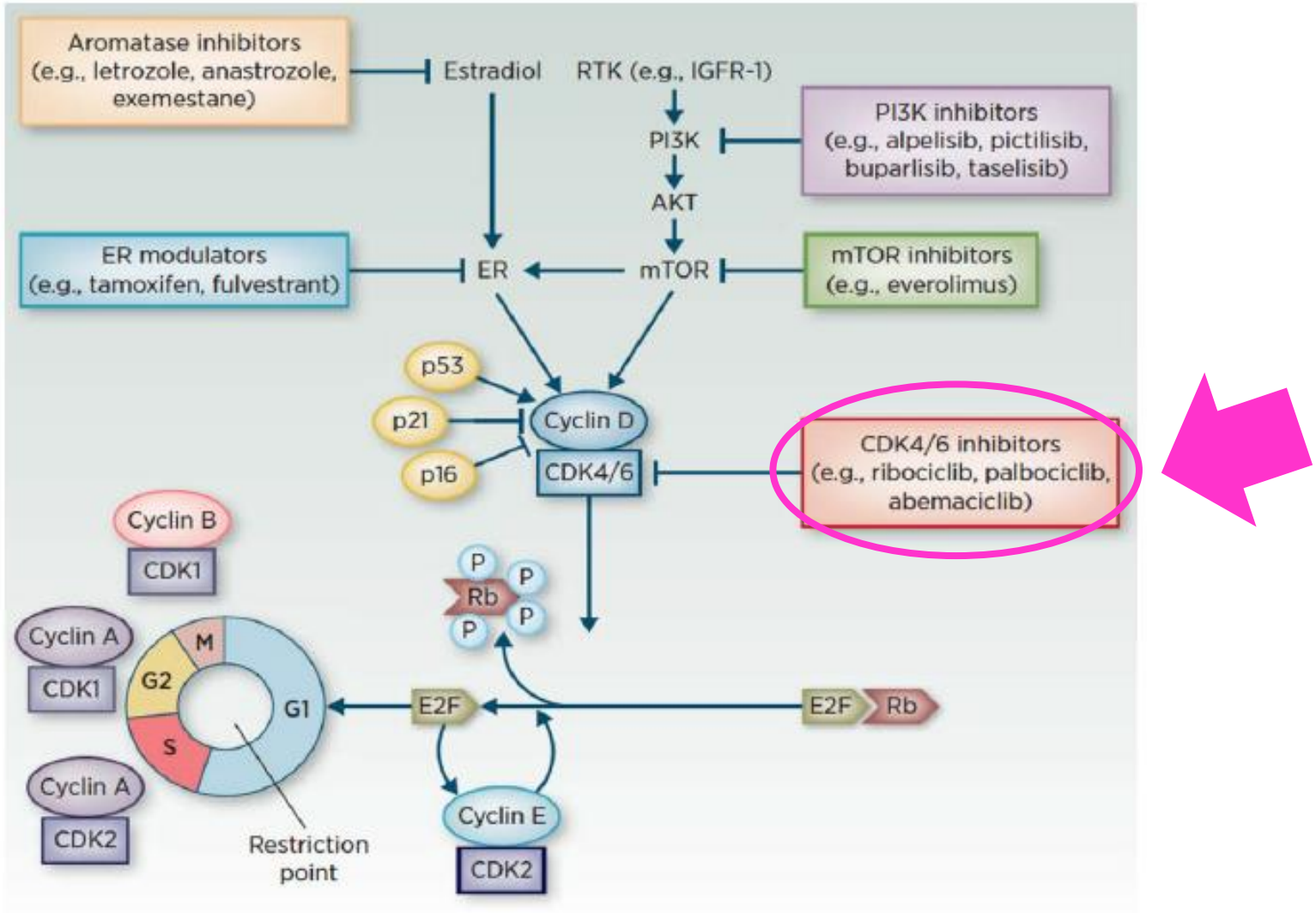
Miglietta F et al., ESMO Open 2022

HR+/HER2- MBC: treatment algorithm



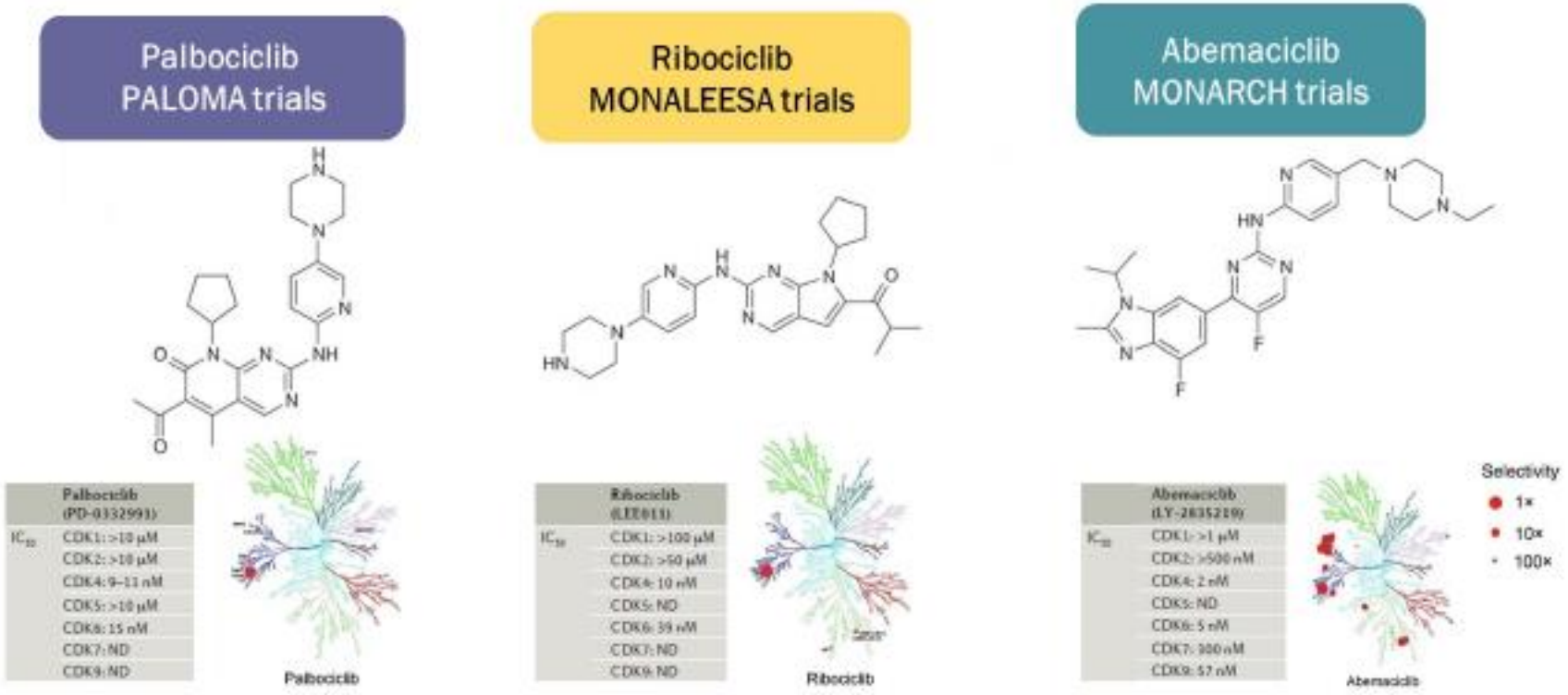
Gennari A et al., Annals of Oncology 2021

HR+/HER2- MBC: rational for CDK4/6 inhibitors



Tripathy D et al., Clin Cancer Res 2017

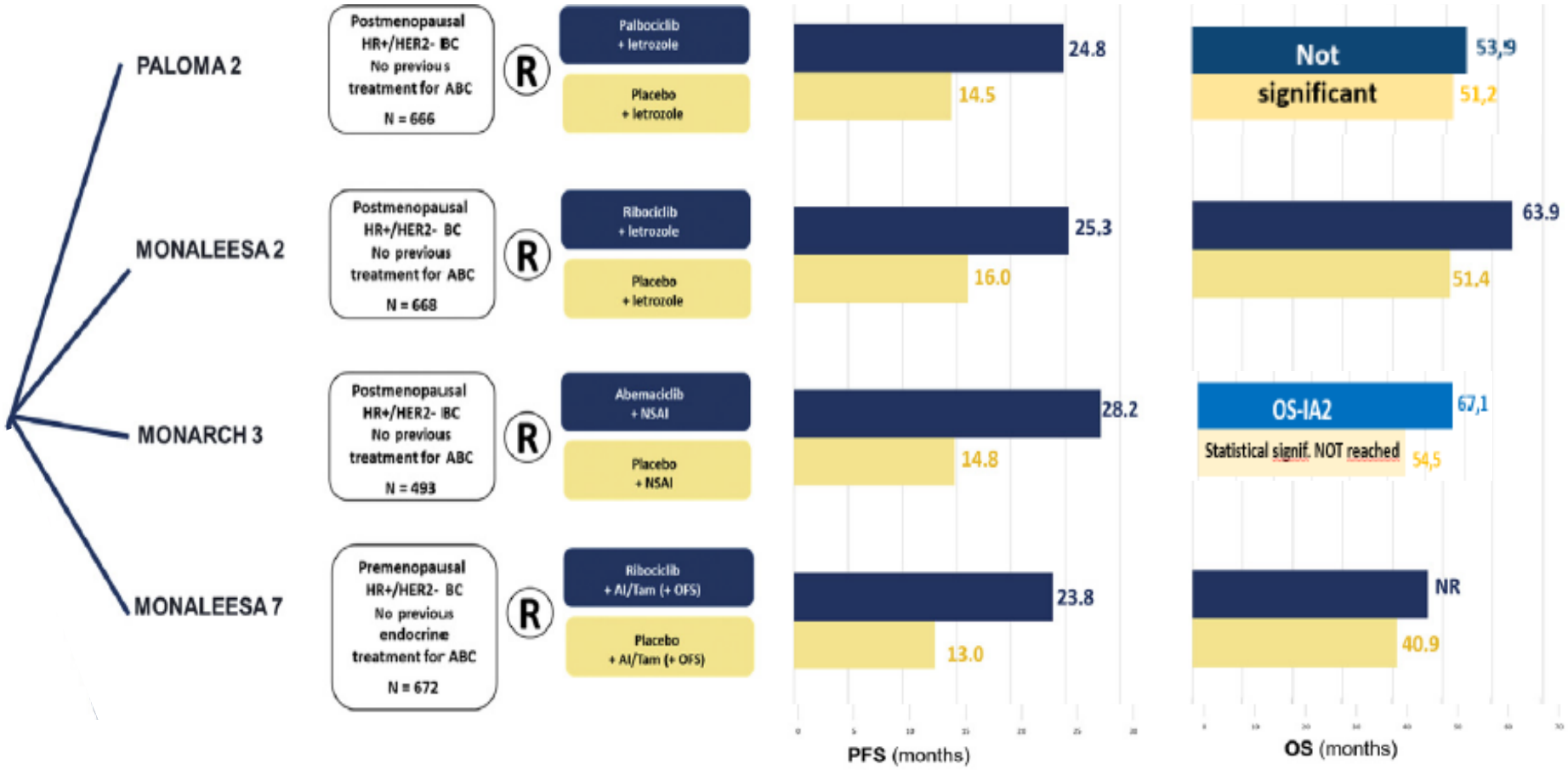
HR+/HER2- MBC: CDK4/6 inhibitors



O'Leary al., Nat rev Oncol 2016

HR+/HER2- MBC: CD4/6i in *endocrine sensitive* pts

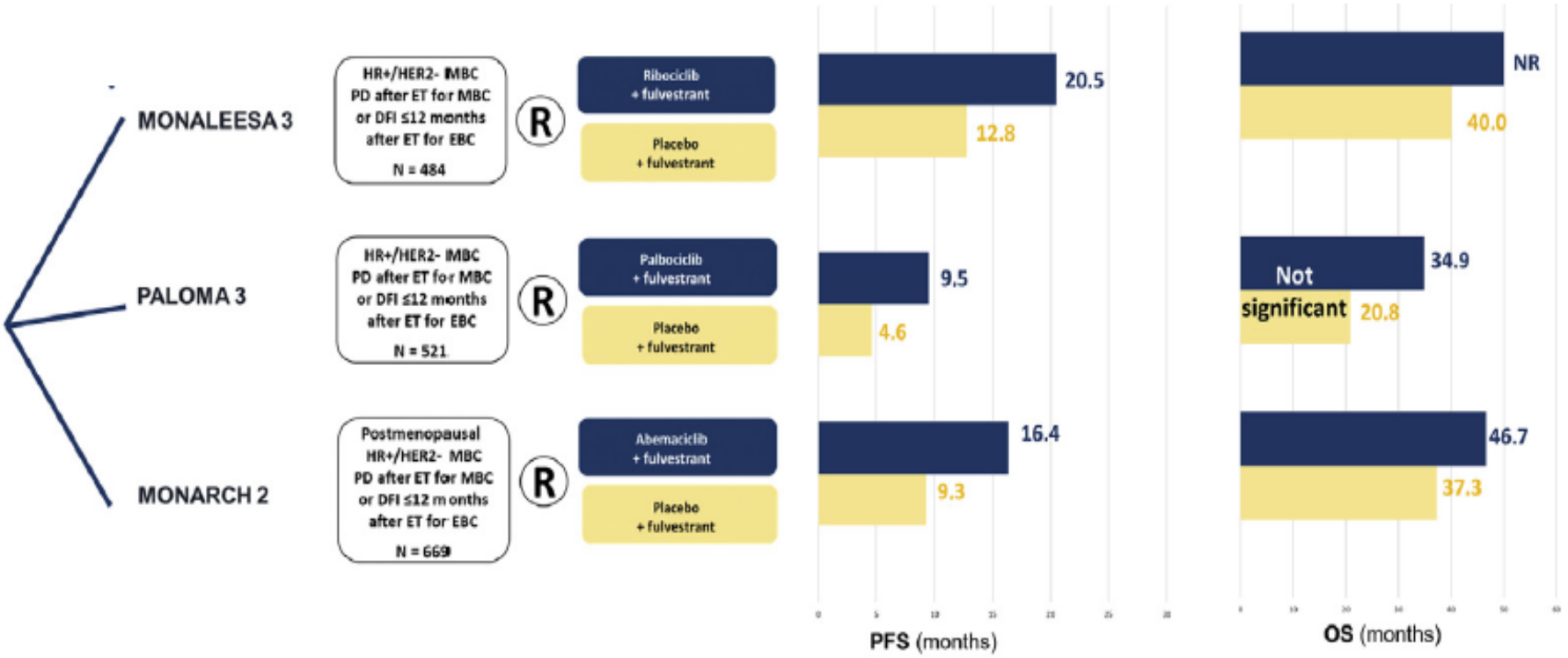
First line (de novo MBC or DFI>12 months from OT for EBC)



Miglietta F et al., ESMO Open 2022

HR+/HER2- MBC: CD4/6i in *endocrine resistant* pts

Second line or first line with DFI<12 months from OT for EBC



Miglietta F et al., ESMO Open 2022

HR+/HER2- MBC: beyond CDK4/6 inhibitors (1)

Pre-CDK4/6i Era

➢ **COMBINATION OF EXEMESTANE AND EVEROLIMUS.**

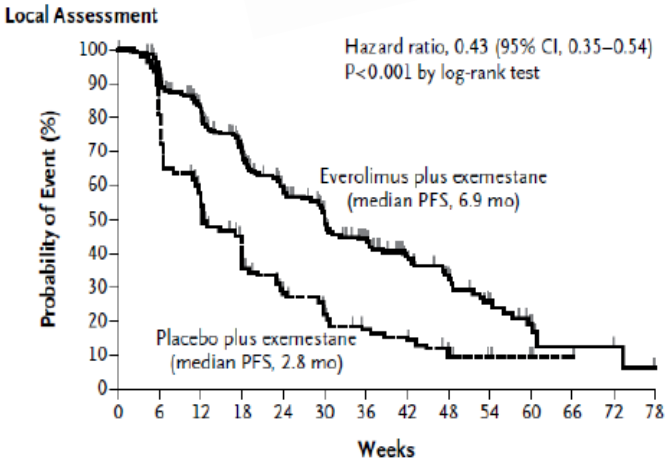
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

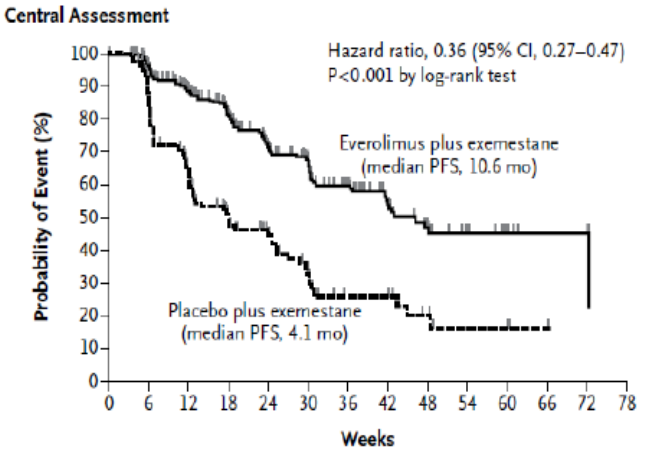
José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

BOLERO-2

CONCLUSIONS

Everolimus combined with an aromatase inhibitor improved progression-free survival in patients with hormone-receptor–positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors. (Funded by Novartis; BOLERO-2 ClinicalTrials.gov number, NCT00863655.)

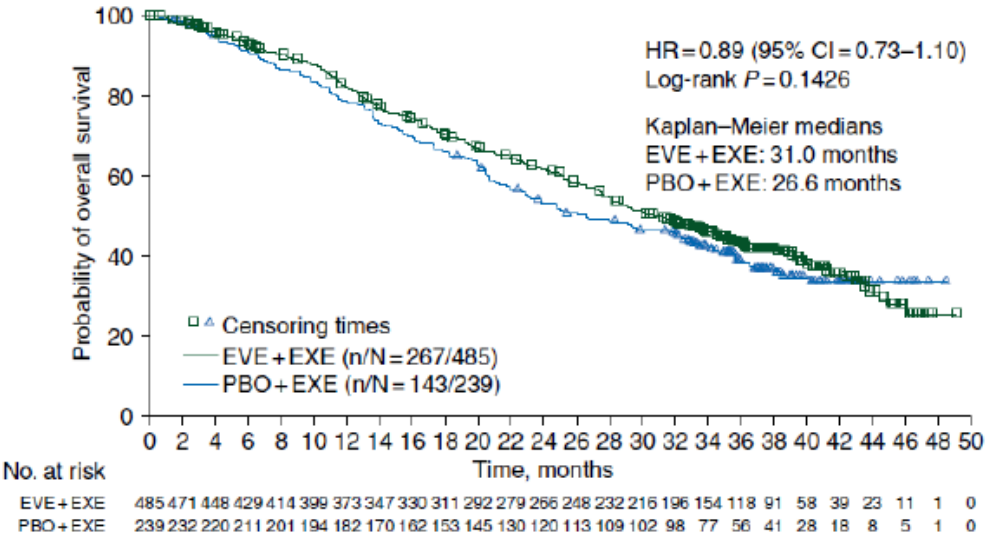




Baselga J et al., NEJM 2012.

Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†

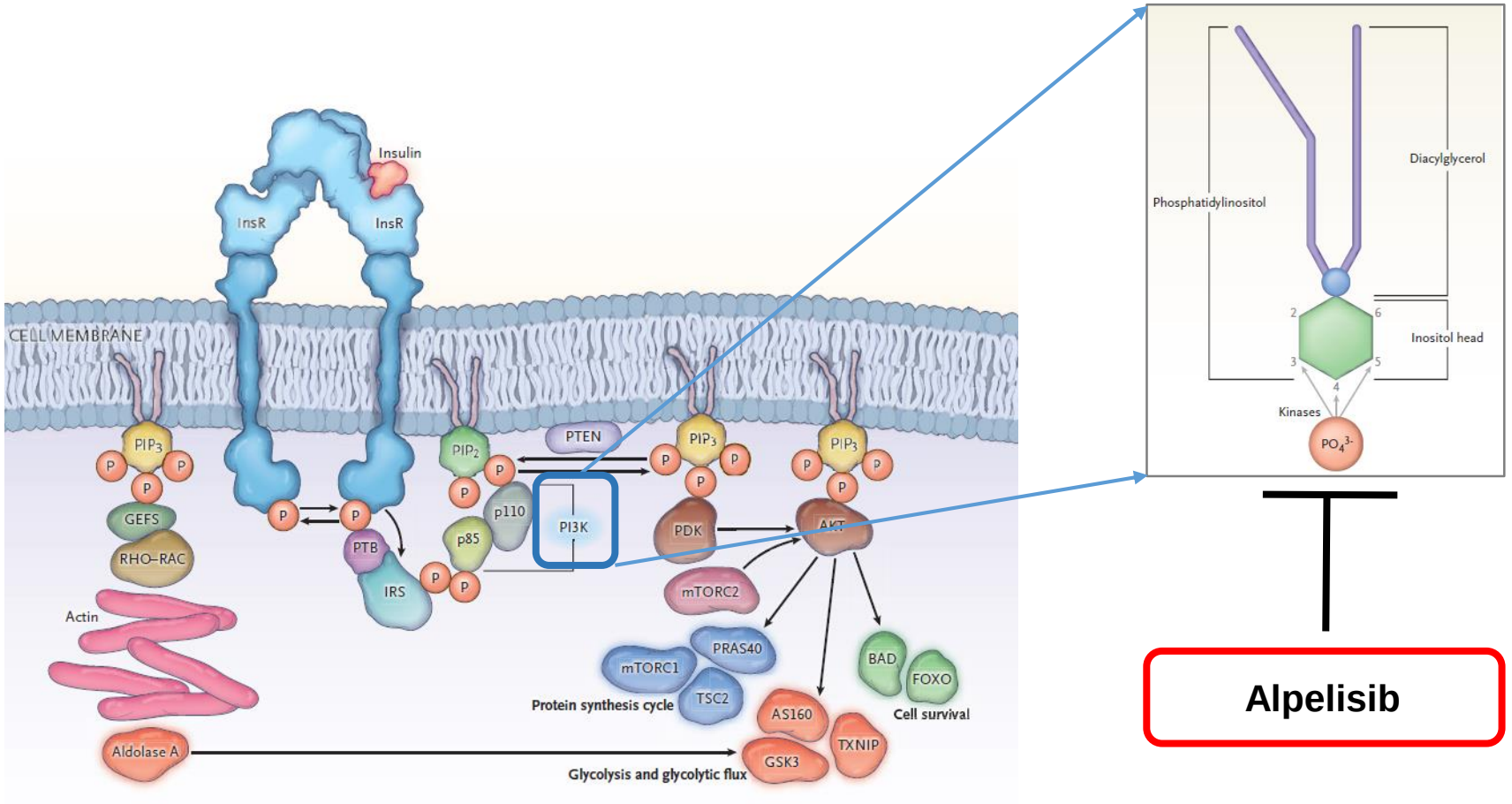
M. Piccart[1*], G. N. Hortobagyi[2], M. Campone[3], K. I. Pritchard[4], F. Lebrun[1], Y. Ito[5], S. Noguchi[6], A. Perez[7], H. S. Rugo[8], I. Deleu[9], H. A. Burris III[10], L. Provencher[11], P. Neven[12], M. Gnant[13], M. Shtivelband[14], C. Wu[15], J. Fan[15], W. Feng[15], T. Taran[15] & J. Baselga[16]



Conclusions: In BOLERO-2, adding EVE to EXE did not confer a statistically significant improvement in the secondary end point OS despite producing a clinically meaningful and statistically significant improvement in the primary end point, PFS (4.6-months prolongation in median PFS; $P < 0.0001$). Ongoing translational research should further refine the

Piccart M et al., Annals of Oncology 2014.

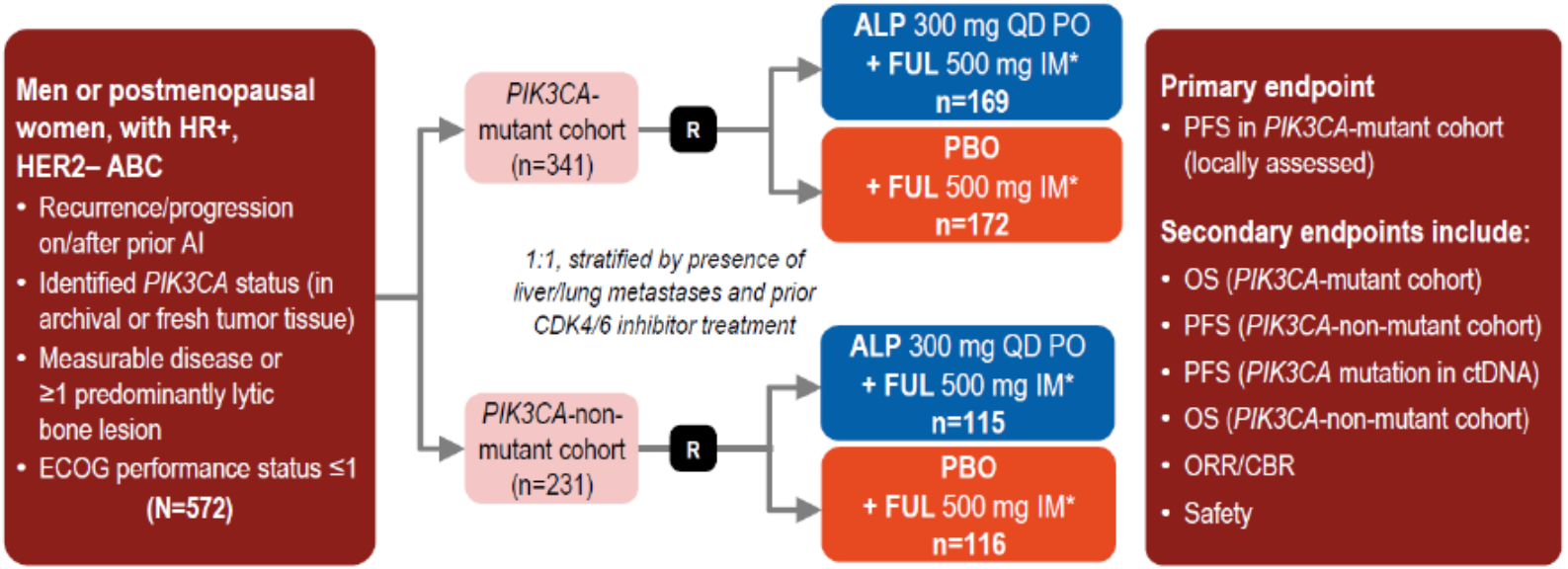
HR+/HER2- MBC: beyond CDK4/6 inhibitors (2)



*~ **40%** of HR+/HER2- MBC have PIK3CA mutation*

Goncalves MD et al., NEJM 2018

SOLAR-1: study design



Andrè F et al., NEJM 2019

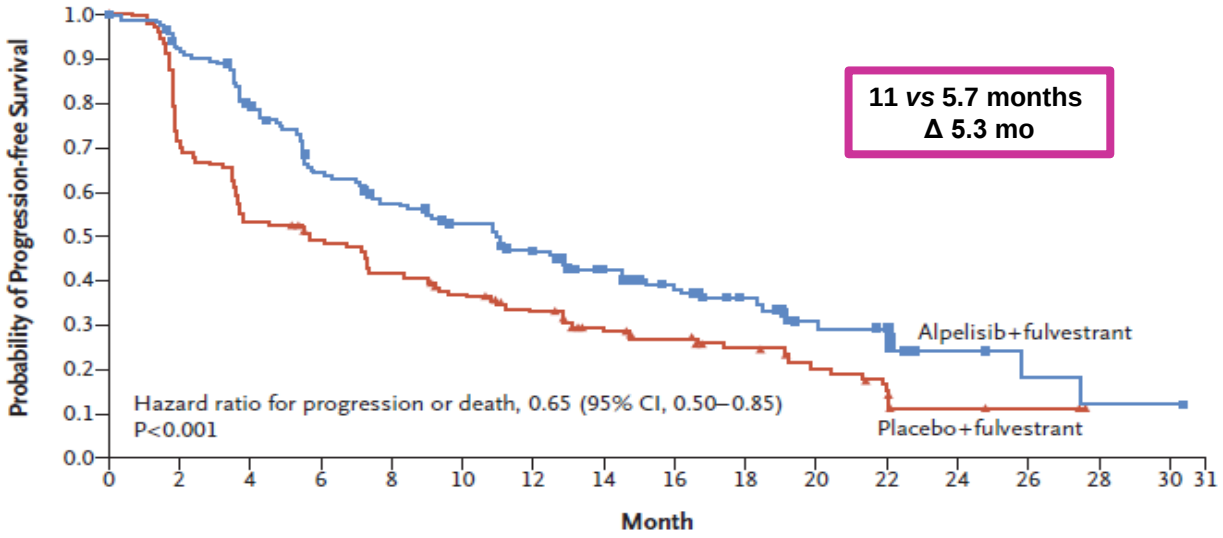
SOLAR-1: patients' characteristics

Characteristic*	*PIK3CA*-mutant		*PIK3CA*-non-mutant	
	Alpelisib + fulvestrant (N=169)†	Placebo + fulvestrant (N=172)‡	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Median age, years (range)	63 (25–87)	64 (38–92)	62 (39–82)	63 (32–88)
Race				
Caucasian	117 (69.2)	109 (63.4)	82 (71.3)	69 (59.5)
Asian	34 (20.1)	40 (23.3)	25 (21.7)	26 (22.4)
Other/unknown	18 (10.7)	23 (13.4)	8 (7.0)	21 (18.1)
Metastatic sites				
Visceral disease	93 (55.0)	100 (58.1)	66 (57.4)	74 (63.8)
Lung/liver metastases	84 (49.7)	86 (50.0)	56 (48.7)	56 (48.3)
Bone-only disease	42 (24.9)	35 (20.3)	26 (22.6)	23 (19.8)
Line of advanced anti-cancer treatment				
First line	88 (52.1)	89 (51.7)	71 (61.7)	62 (53.4)
Second line	79 (46.7)	82 (47.7)	42 (36.5)	53 (45.7)
Endocrine resistance status§				
Primary resistance	23 (13.6)	22 (12.8)	31 (27.0)	26 (22.4)
Secondary resistance	120 (71.0)	127 (73.8)	66 (57.4)	65 (56.0)
Sensitive	20 (11.8)	19 (11.0)	16 (13.9)	20 (17.2)
Prior chemotherapy				
Neo-adjuvant	25 (14.8)	29 (16.9)	20 (17.4)	23 (19.8)
Adjuvant	78 (46.2)	86 (50.0)	64 (55.7)	58 (50.0)
Prior CDK4/6 inhibitor treatment	9 (5.3)	11 (6.4)	7 (6.1)	8 (6.9)

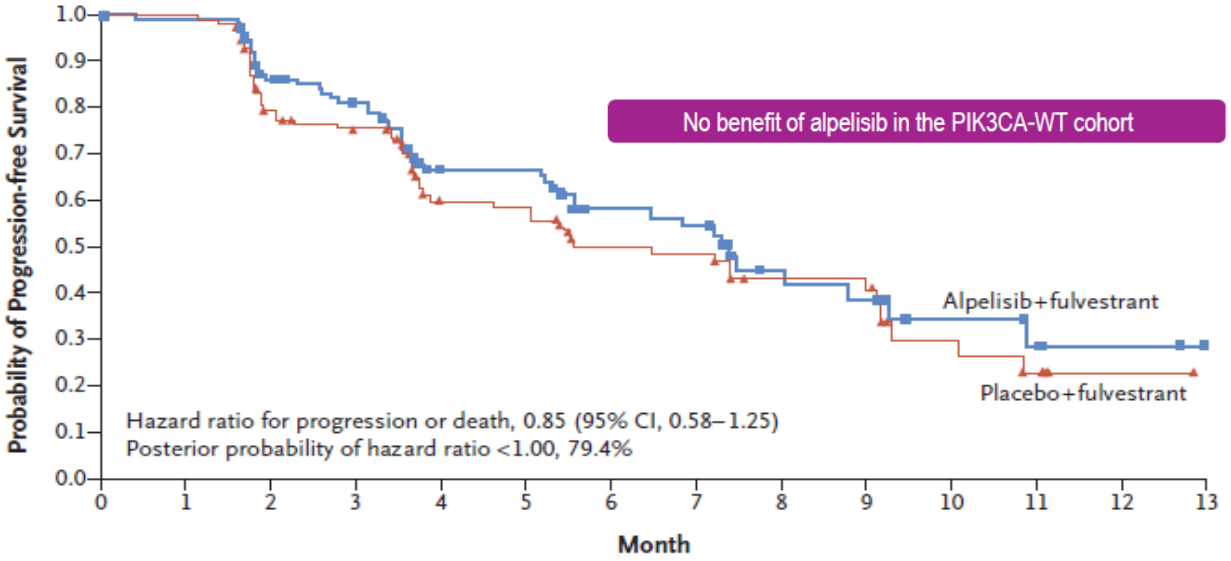
Andrè F et al., NEJM 2019

SOLAR-1: PFS

PIK3CA-MUT cohort

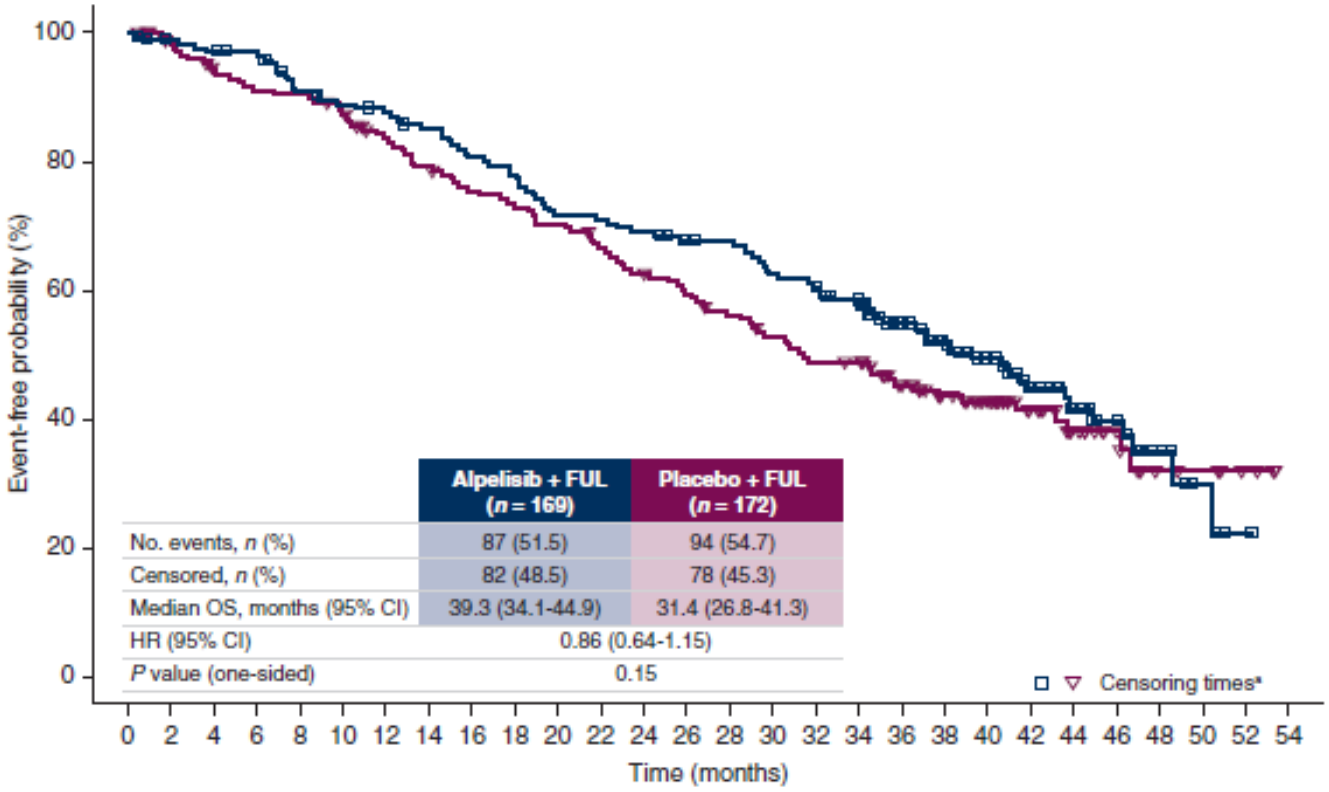


PIK3CA-WT cohort



Andrè F et al., NEJM 2019

SOLAR-1: OS in PIK3CA mut



	Alpelisib + FUL (*n* = 169)	Placebo + FUL (*n* = 172)
No. events, *n* (%)	87 (51.5)	94 (54.7)
Censored, *n* (%)	82 (48.5)	78 (45.3)
Median OS, months (95% CI)	39.3 (34.1-44.9)	31.4 (26.8-41.3)
HR (95% CI)	0.86 (0.64-1.15)	
P value (one-sided)	0.15	

7.9-month numeric improvement in median OS

Andrè F et al., Ann Oncol 2021

SOLAR-1: safety

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

Andrè F et al., NEJM 2019

Alpelisib regulatory positioning

24 May 2019 – alpelisib + fulvestrant for postmenopausal HR+/HER2- ABC pts with PIK3CA mutation detected by a FDA-approved test **following progression on or after an endocrine-based regimen**

EMA

28 May 2020 – alpelisib + fulvestrant for postmenopausal HR+/HER2- ABC pts with PIK3CA mutation after disease progression **following endocrine therapy as monotherapy**


SERIE GENERALE

Anno 161° - Numero 294

GAZZETTA UFFICIALE

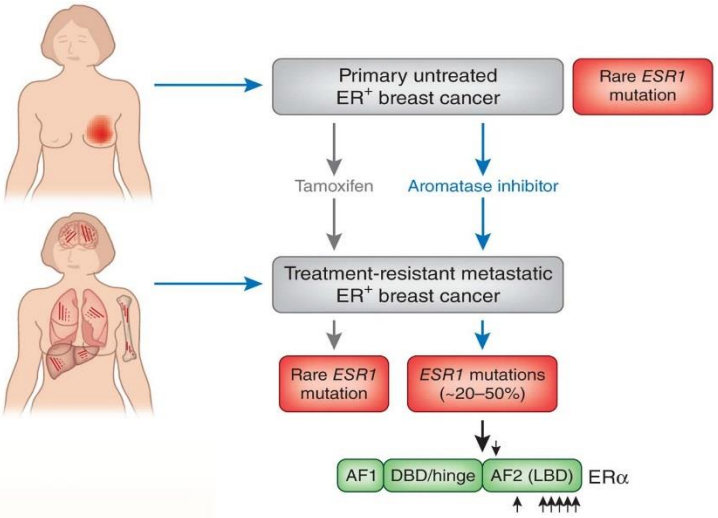
DELLA REPUBBLICA ITALIANA

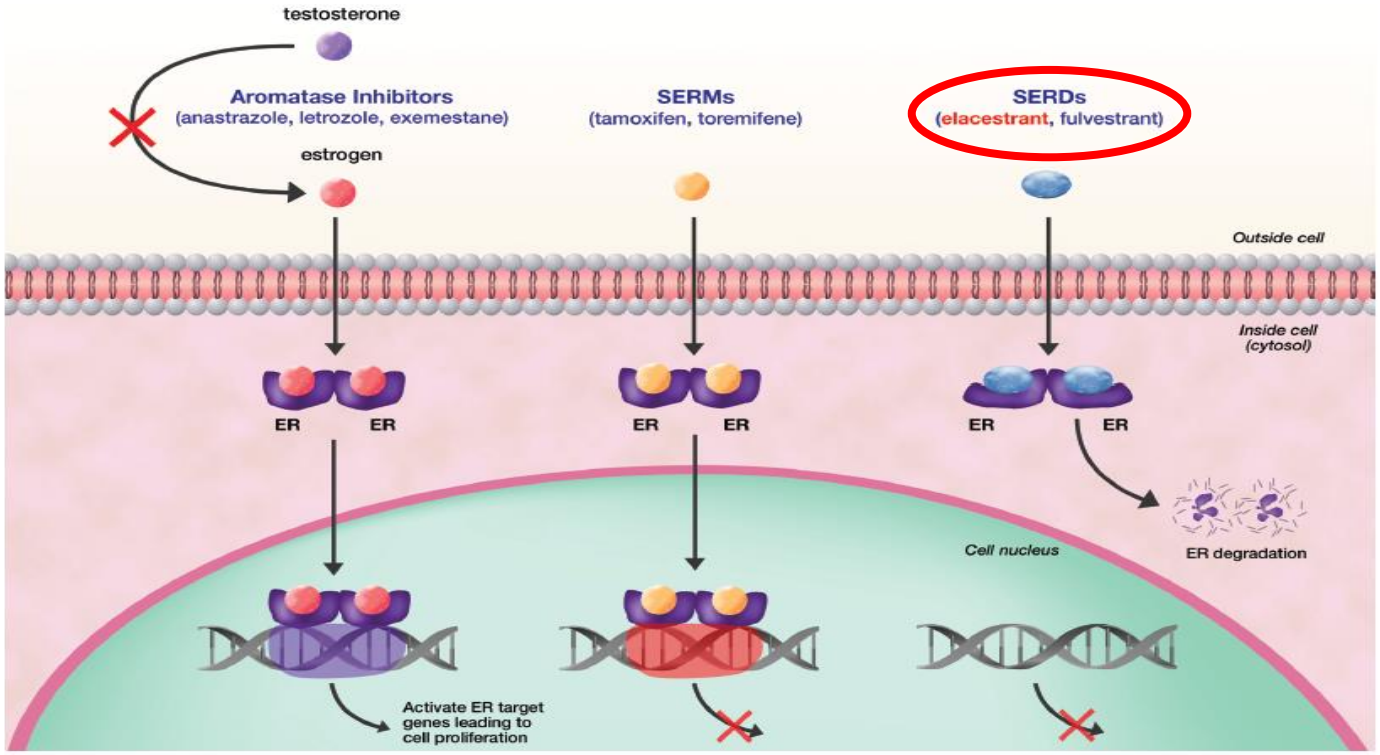
PARTE PRIMA — Roma - Giovedì, 26 novembre 2020

Alpelisib + fulvestrant è indicato per pz in postmenopausa affetti da HR+/HER2- ABC, con mutazione di PIK3CA, **dopo progressione di malattia successiva a terapia endocrina come monoterapia**

HR+/HER2- MBC: beyond CDK4/6 inhibitors (3)

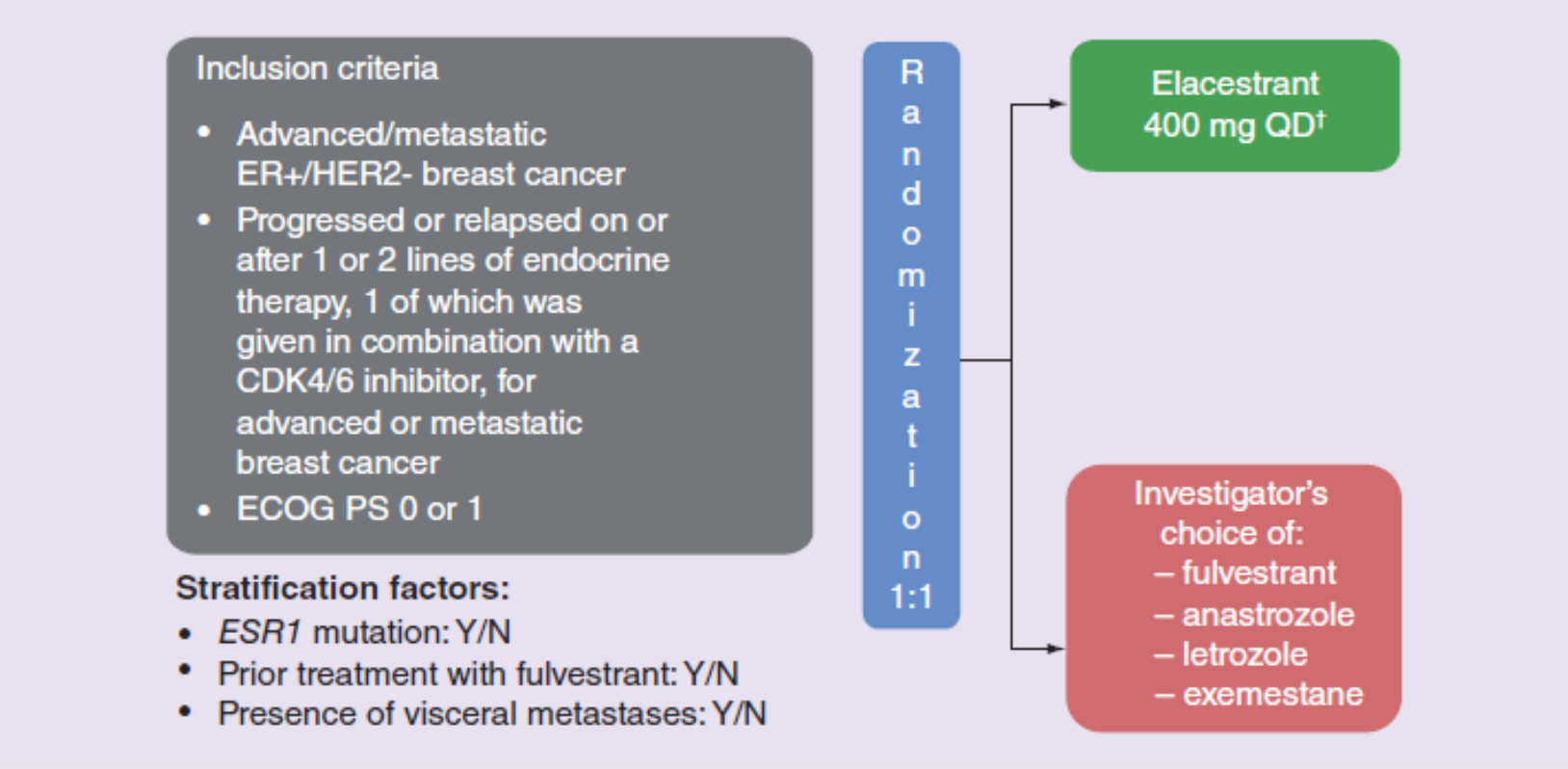
- Mutations in ESR1 have been identified in nearly **20-50% of ET and CDK4/6i** resistant tumors and confer ligand-independent activation of the ER pathway
- ESR1 mutant HR+/HER2- ABC is associated with **aggressive disease biology and with shorter OS** relative to the WT ESR1
- ESR1 mutations are a resistance mutation induced by the selective pressure of prior AI therapy in ABC
- These mutations do not confer resistance to selective estrogen down-regulator (SERD) therapy





Oesterreich S & Davidson NE, Nat Genet 2013
Bardia A, Future Oncol 2019

EMERALD: study design



Bardia A, SABCS 2022

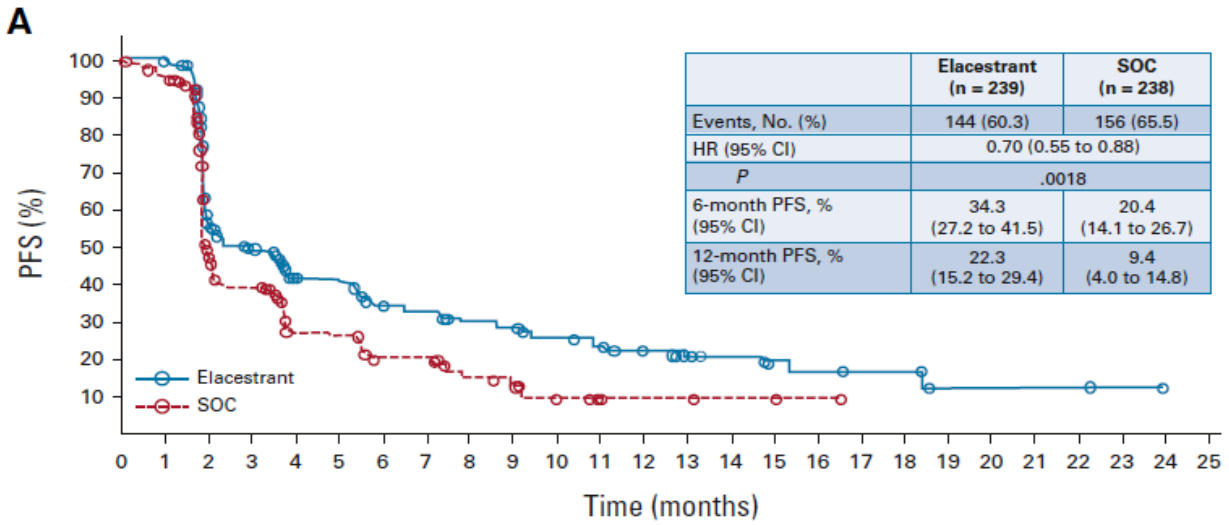
EMERALD trial: patients' characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%)				
Female	233 (97.5)	115 (100)	238 (99.6)	113 (100)
Male	6 (2.5)	0	1 (0.4)	0
ECOG PS, n (%)				
0	143 (59.8)	67 (58.3)	135 (56.5)	62 (54.9)
1	96 (40.2)	48 (41.7)	103 (43.1)	51 (45.1)
>1	0	0	1 (0.4)	0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%)				
1	129 (54.0)	73 (63.5)	142 (59.4)	69 (61.1)
2	110 (46.0)	42 (36.5)	97 (40.6)	44 (38.9)
Type of prior endocrine therapy,** n (%)				
Fulvestrant	70 (29.3)	27 (23.5)	75 (31.4)	28 (24.8)
AI	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
Number of prior lines of chemotherapy,** n (%)				
0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
1	48 (20.1)	26 (22.6)	59 (24.7)	32 (28.3)

Bidard FC et al., JCO 2022

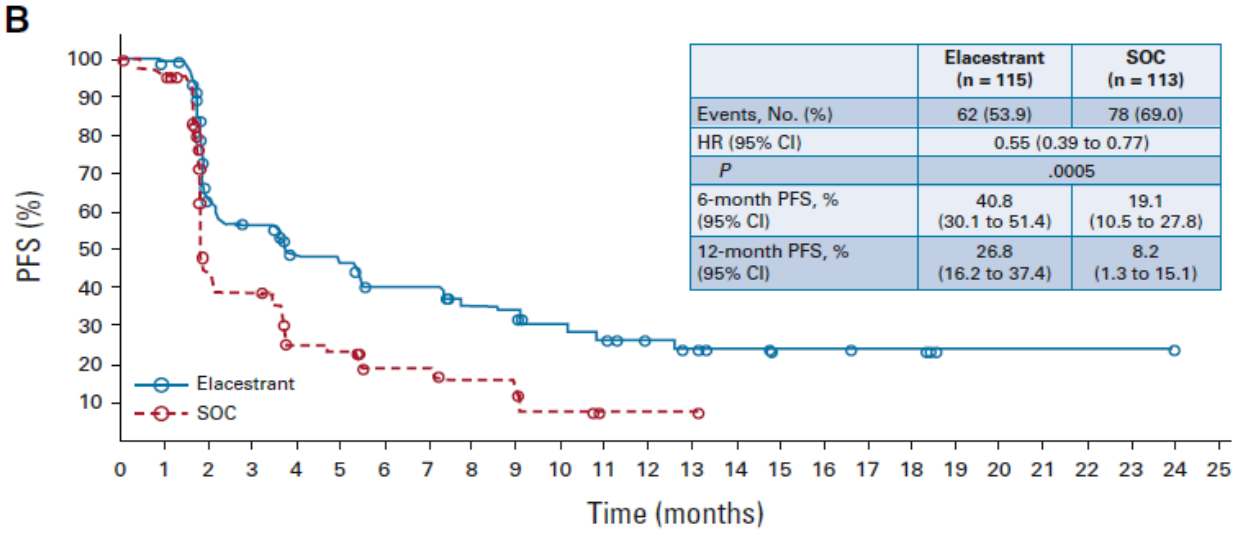
EMERALD trial: PFS

All patients



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

Patients with ESR1 mut

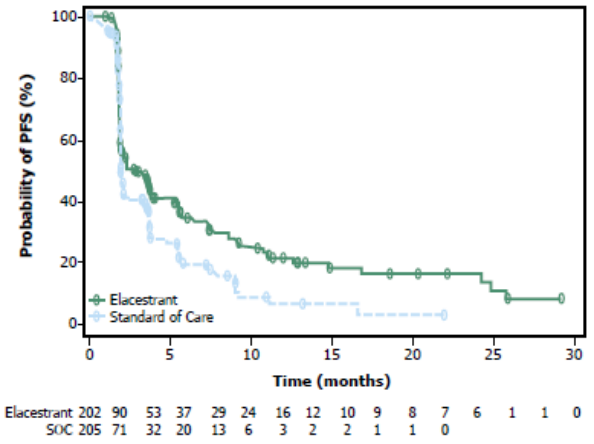


	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

Bidard FC et al., JCO 2022

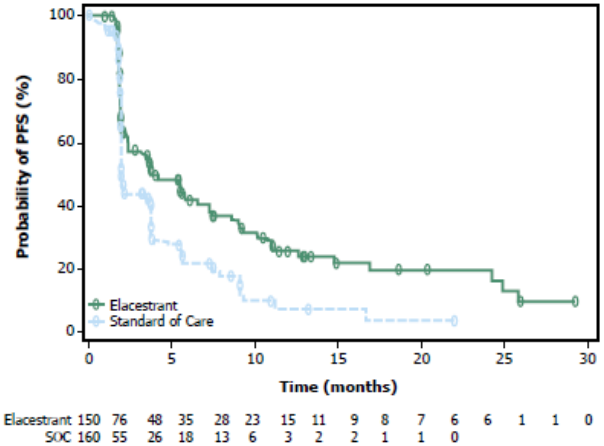
PFS by duration of CDK4/6i: in all patients

At least 6 mo CDK4/6i



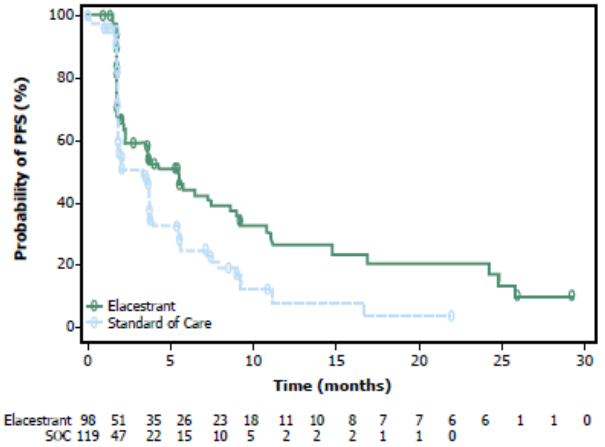
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i

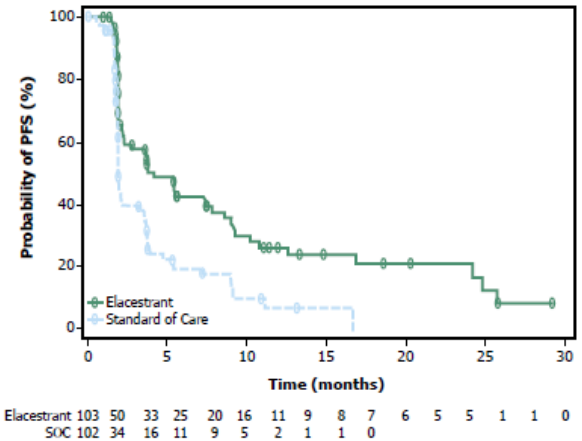


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Bardia A, SABCS 2022

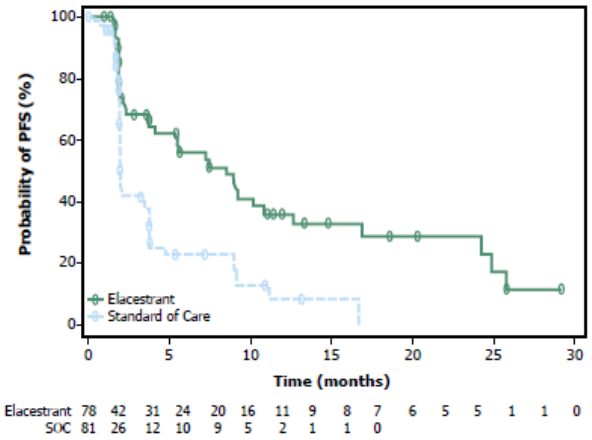
PFS by duration of CDK4/6i: in pts with ESR1-mut MBC

At least 6 mo CDK4/6i



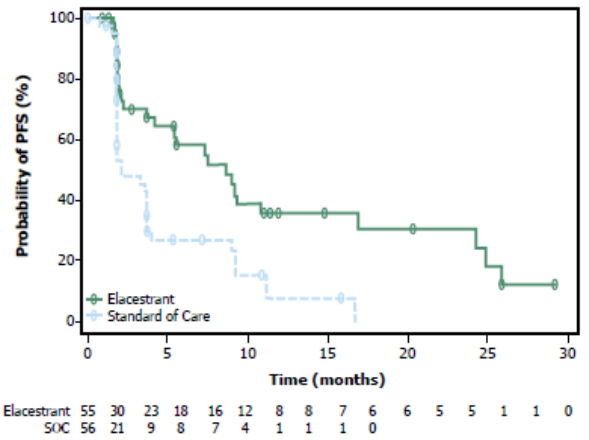
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia A, SABCS 2022

EMERALD trial: safety

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Bardia A, SABCS 2022

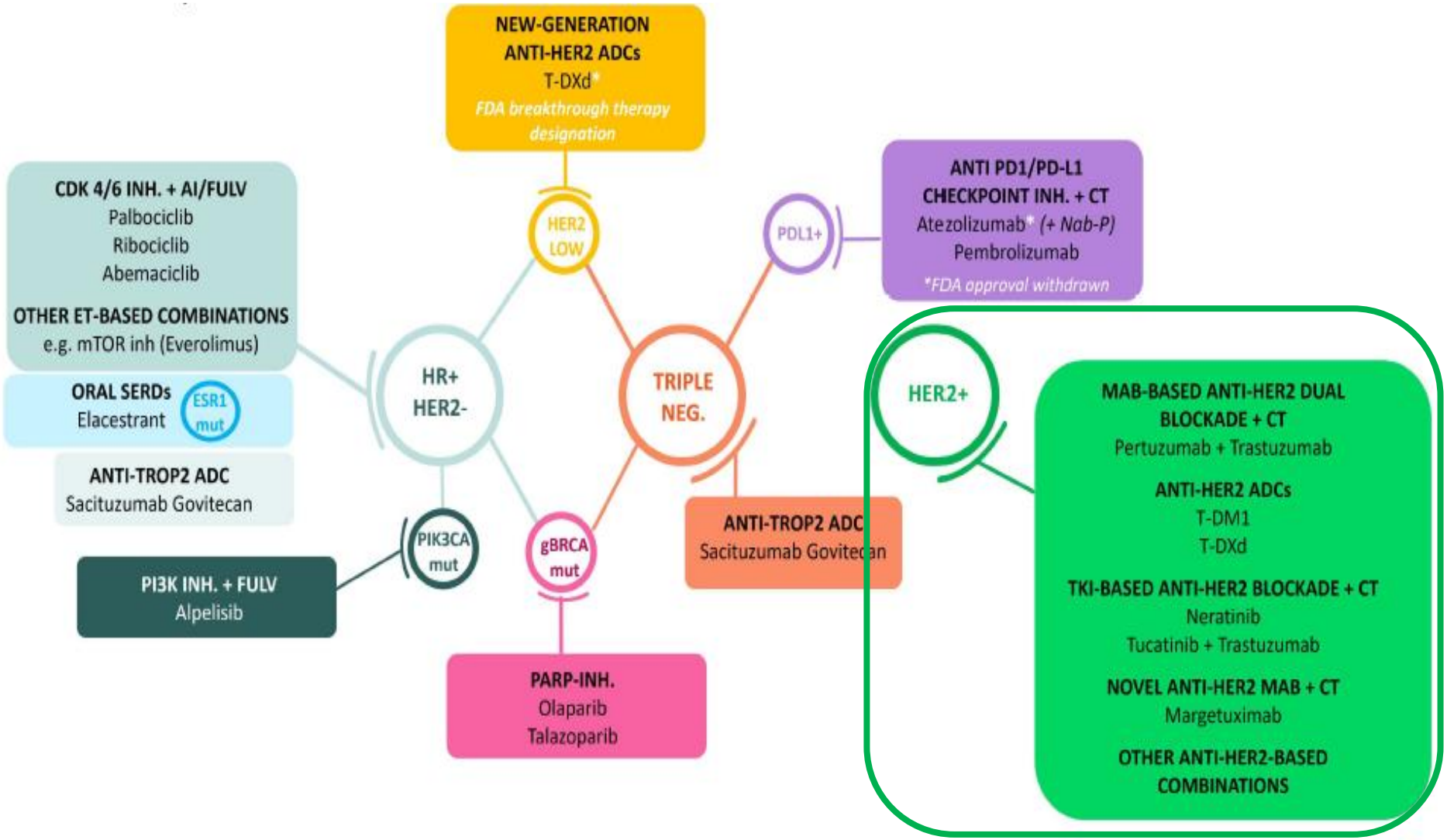
Conclusions:

- **CDK4/6i** represent the **current standard of care for the front-line therapy** of HR+/HER2- MBC
  - both in postmenopuasal and premenopausal setting
  - both in endocrine sensitive and endocrine resistant setting

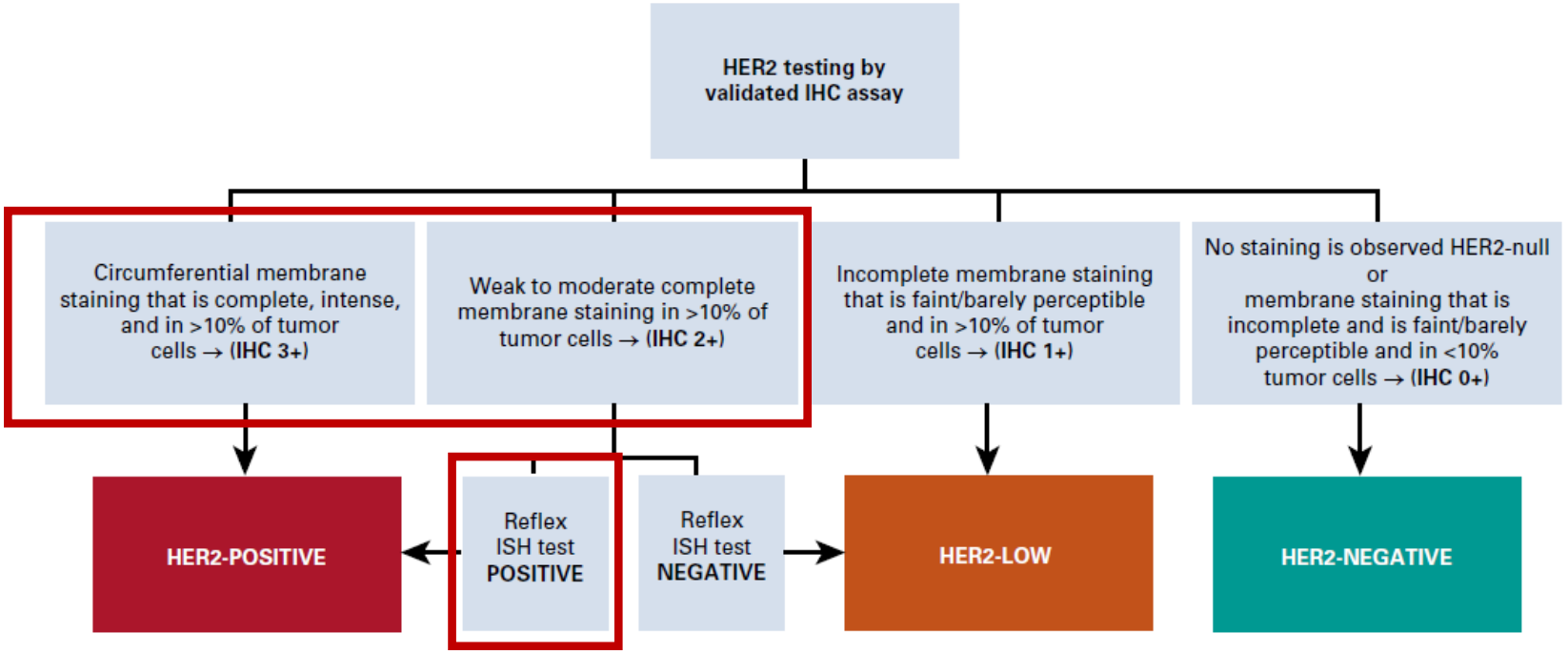
- The clinical value of PI3K inhibitors in PIK3CA mutated patients with endocrine-resistant disease is established. The regulatory scenario of **alpelisib currently precludes patients with PIK3CA-mutated disease progressing to CDK4/6i+AI** to get access to this treatment strategy → alpelisib is only a virtual option with no actual positioning.

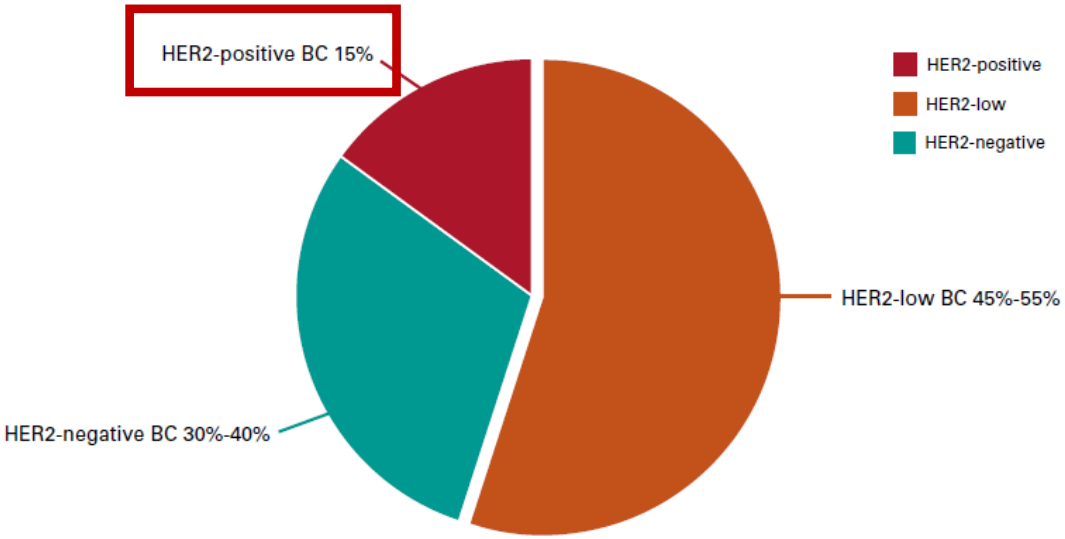
- BC eventually develop hormonal resistance mainly through the development of ESR1 mutations. **Oral SERDs**, such as Elacestrant, can become **important endocrine monotherapy agents in second/third line**.

HER2+ MBC



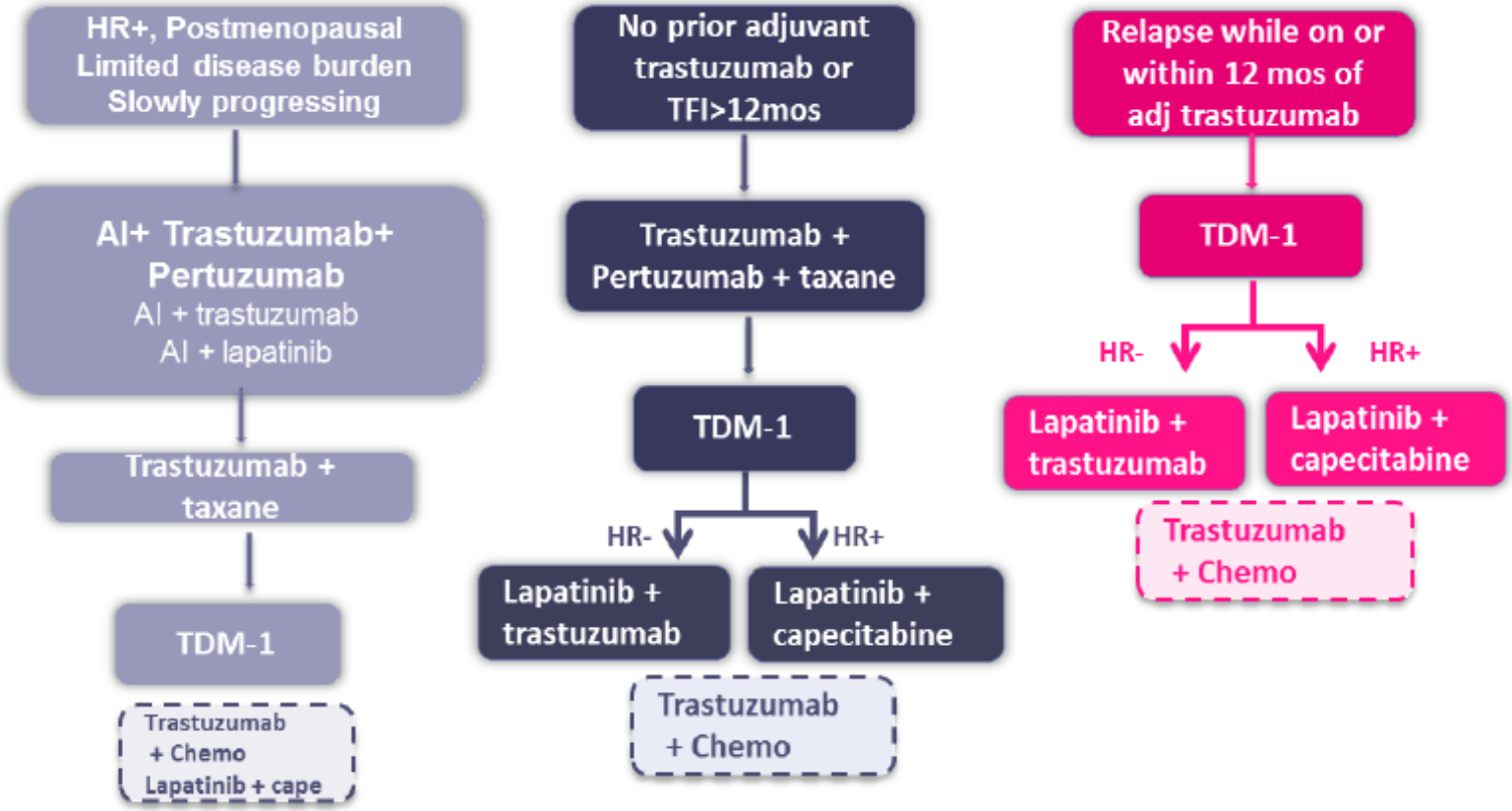
Miglietta F et al., ESMO Open 2022





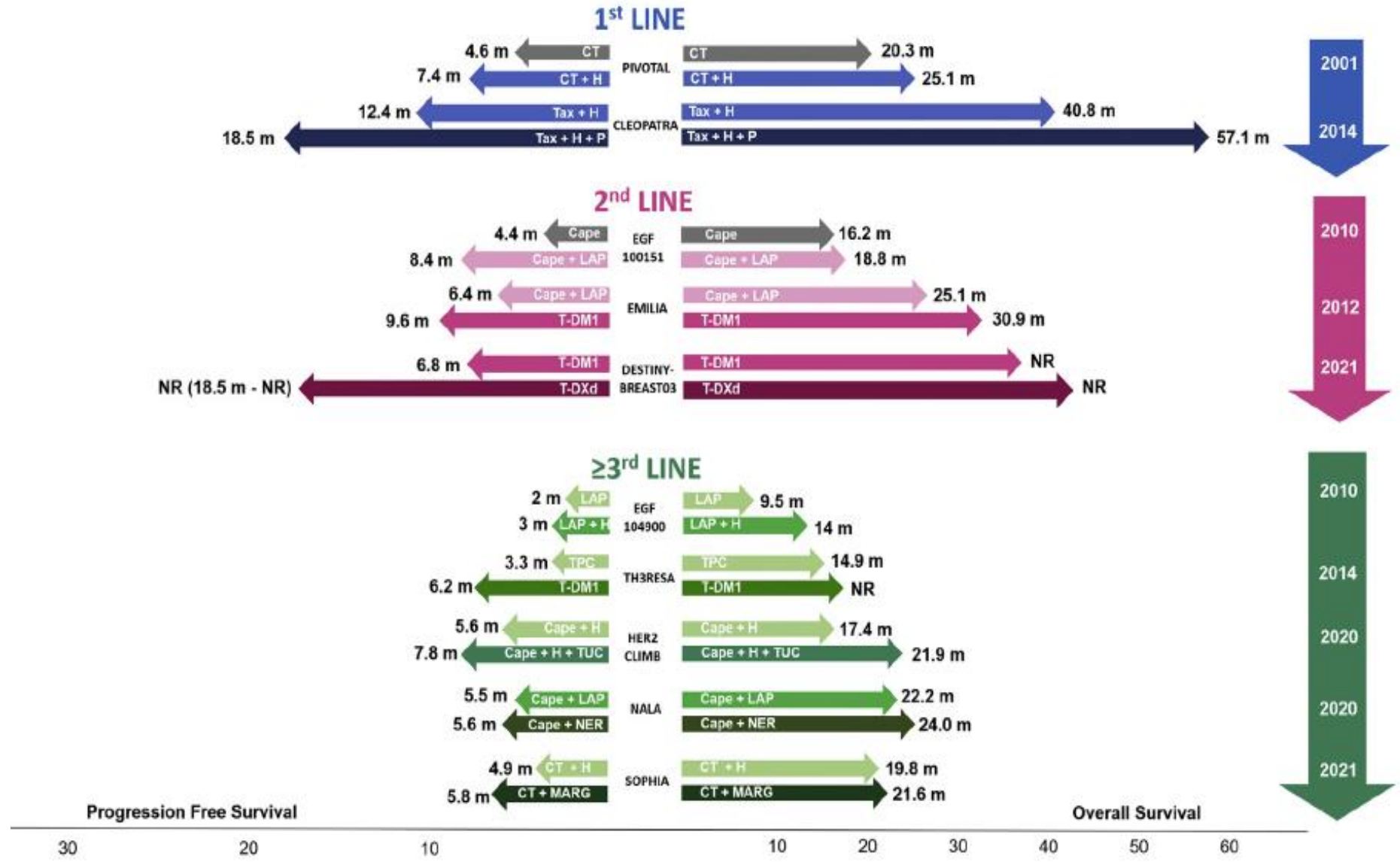
Tarantino P et al., JCO 2022

HER2+ MBC: treatment algorithm



Courtesy by MV Dieci

HER2+ MBC: an evolving treatment landscape



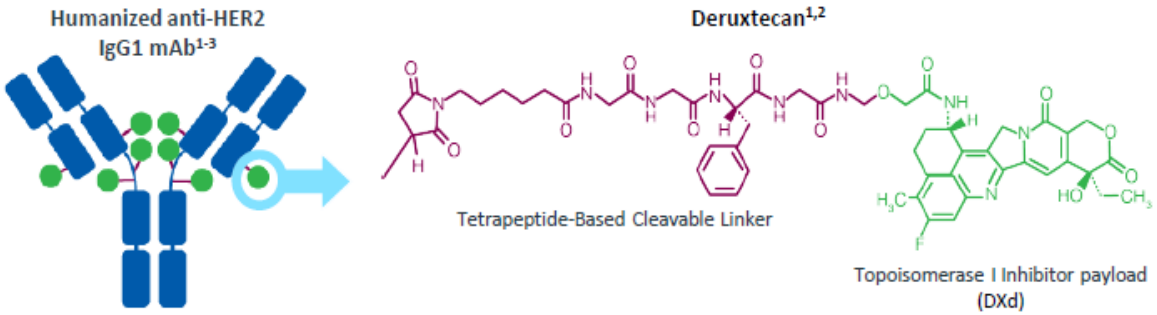
Miglietta F et al., ESMO Open 2022

The "New" Antibody-Drug Conjugates (ADCs):

Trastuzumab deruxtecan

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload MOA: topoisomerase I inhibitor

High potency of payload

High drug to antibody ratio ≈ 8

Payload with short systemic half-life

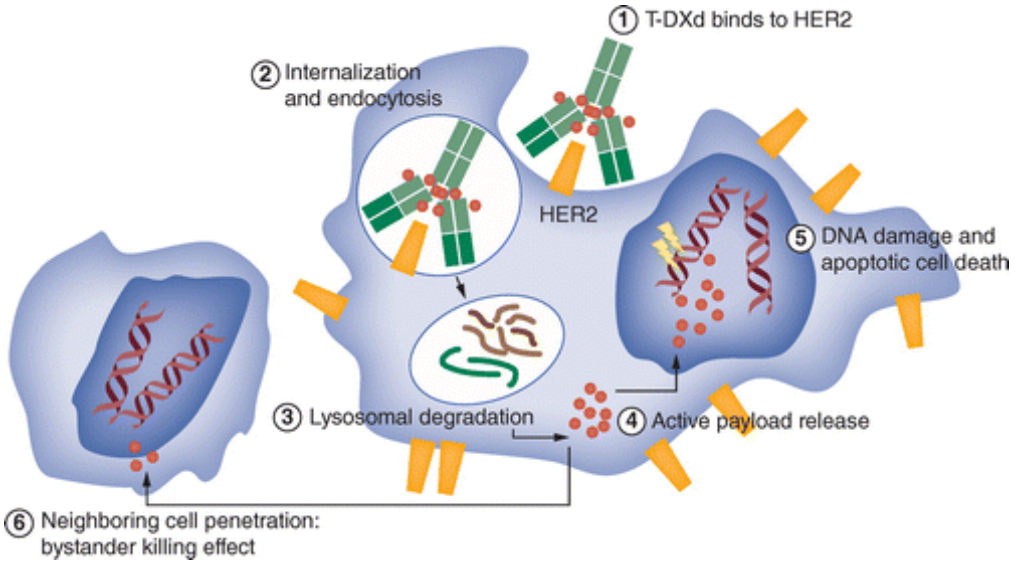
Stable linker-payload

Tumor-selective cleavable linker

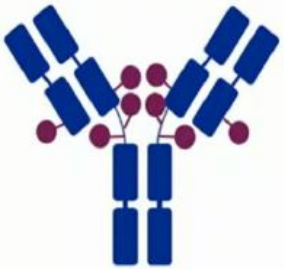
Membrane-permeable payload

Krop et al., SABCS 2021

Mechanism of action



Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]

Rinnertalet G et al., Int Mol Sci 2019; Cortes J et al., ESMO 2021

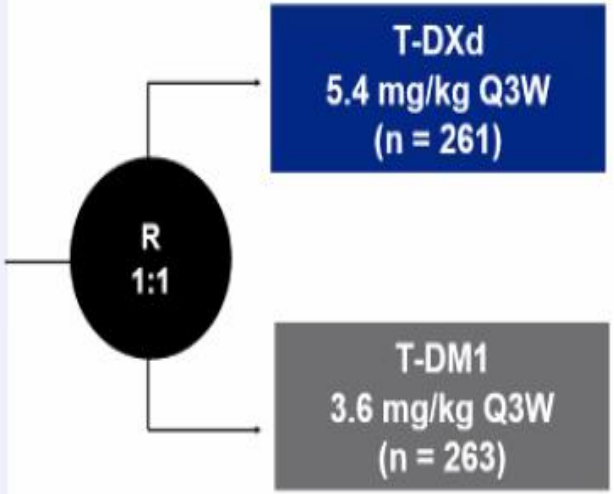
DESTINY-Breast03: study design

Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

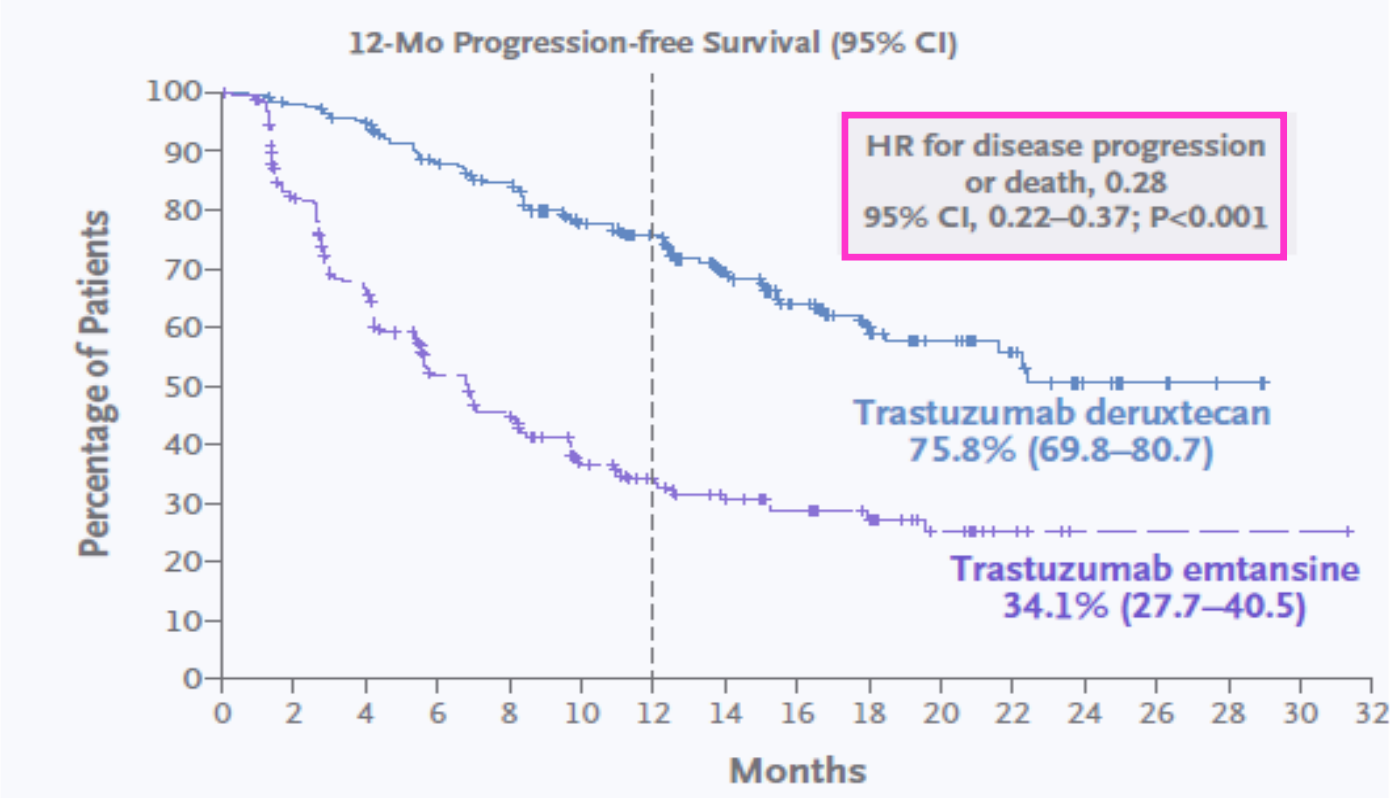
Cortès J ESMO 2021; Cortès J et al., NEJM 2022

DESTINY-Breast03: patients' characteristics

	T-DXd (n=261)	T-DM1 (n=263)
Age, median (yrs)	54.3 (27.9-93.1)	54.2 (20.2-83.0)
HER2 3+ HER2 2+ (ISH ampl)	89.7 9.6	88.2 11.4
HR+	50.2	21.0
History of Brain Mets	23.8	19.8
Visceral disease	70.5	70.3
Prior Tx for MBC	92.0	89.0
Prior lines in MBC (incl rapid PD as 1 line) 0 1 2+	 0.8 49.8 49.4	 1.1 46.8 52
Prior Trastuzumab	99.6	99.6
Prior Pertuzumab	62.1	60.1
Prior anti-HER2 TKI	16.1	13.7

Cortès J ESMO 2021; Cortès J et al., NEJM 2022

DESTINY-Breast03: PFS

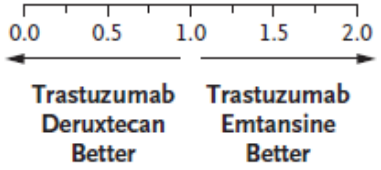


Median FU for T-DXd was 16,2 months and for T-DM1 was 15.3 months

Cortès J et al., NEJM 2022

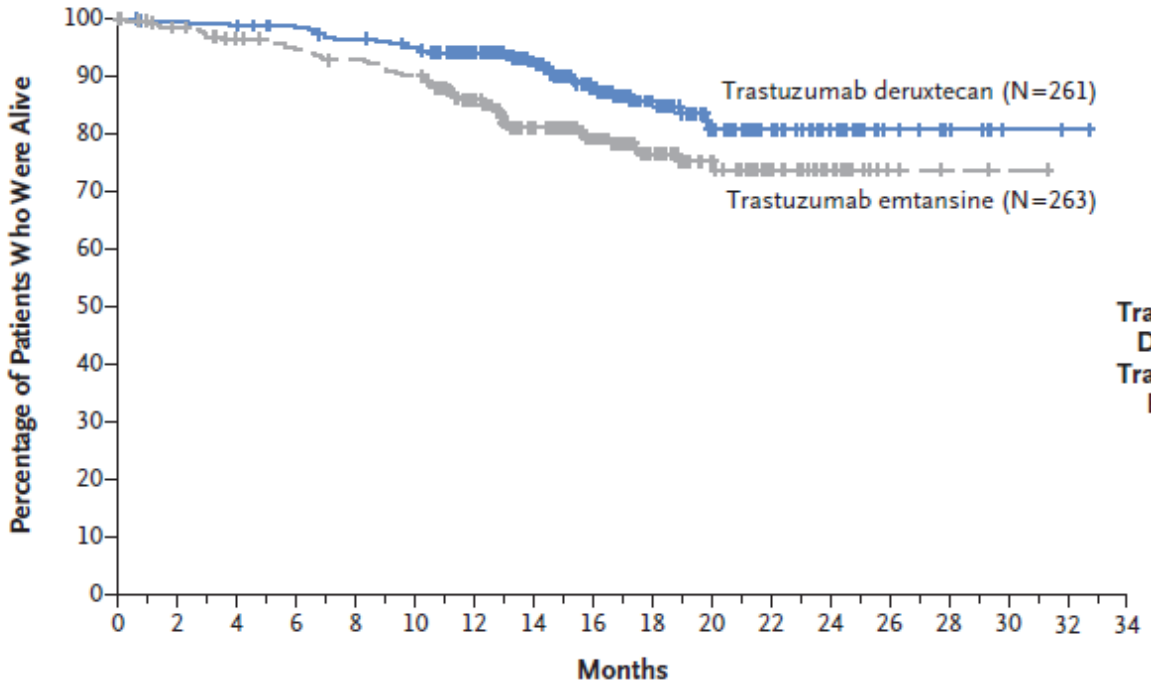
DESTINY-Breast03: PFS in subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI) *mo*		Hazard Ratio for Disease Progression or Death (95% CI)
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



Cortès J et al., NEJM 2022

DESTINY-Breast03: OS



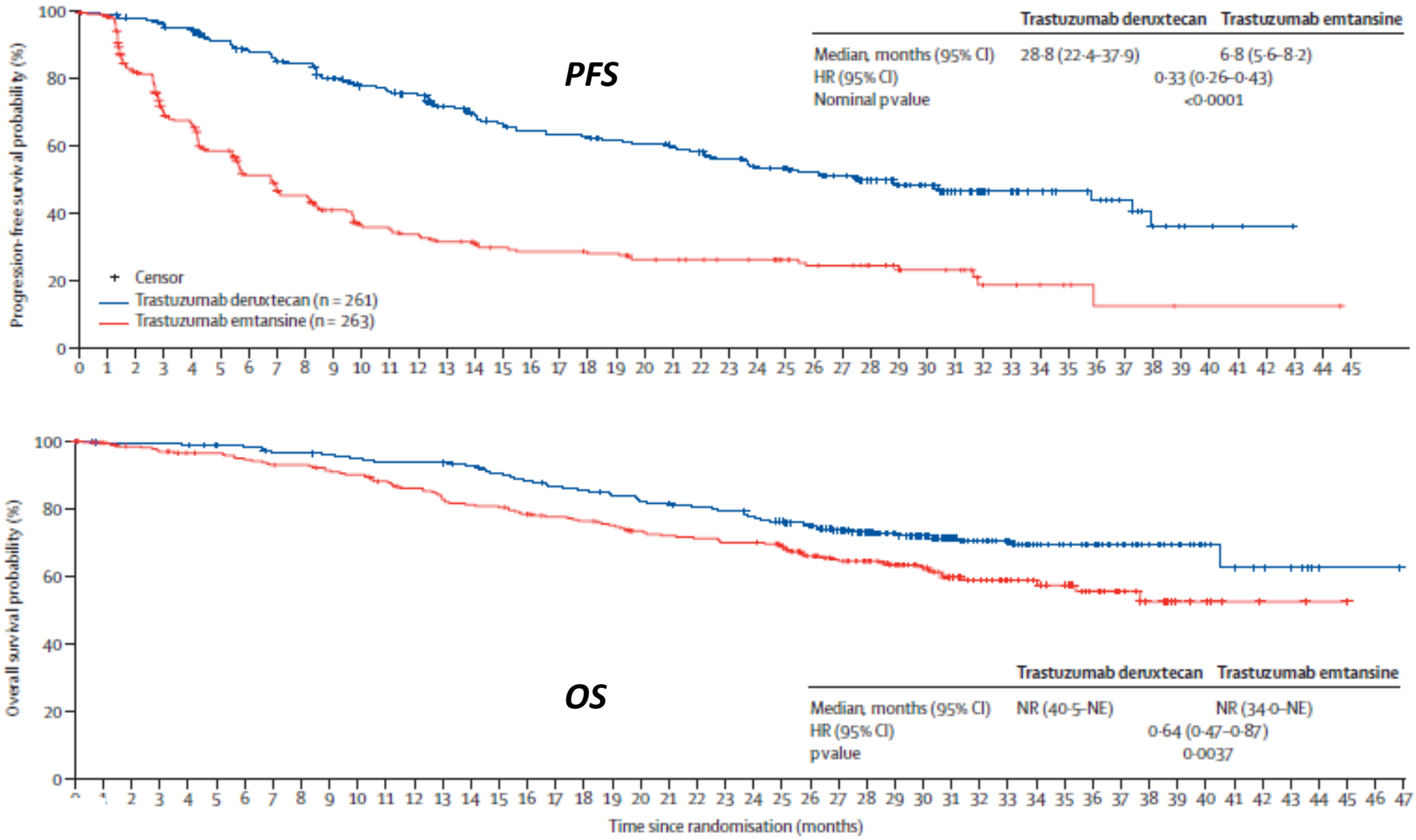
	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

Cortès J et al., NEJM 2022

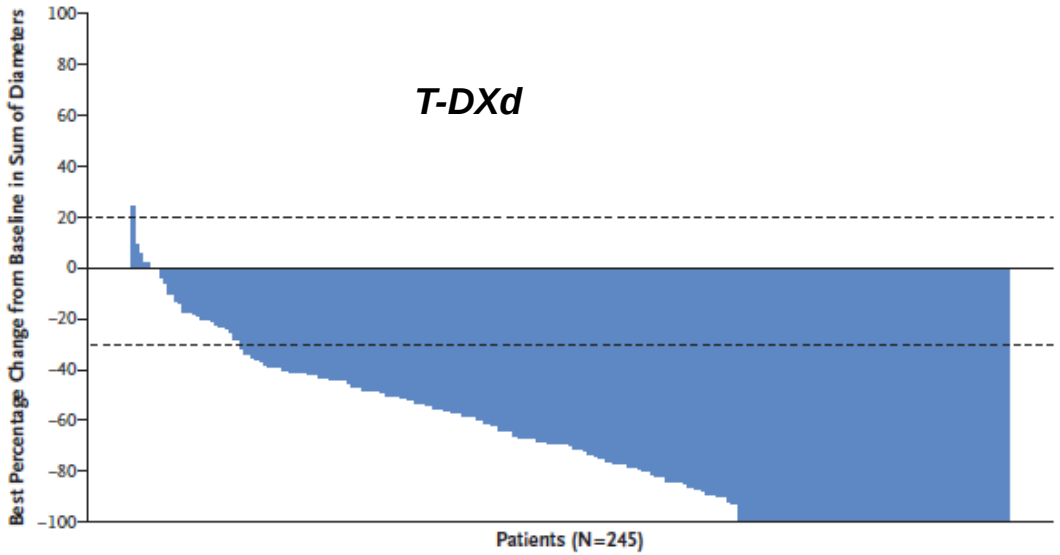
DESTINY-Breast03: updated results

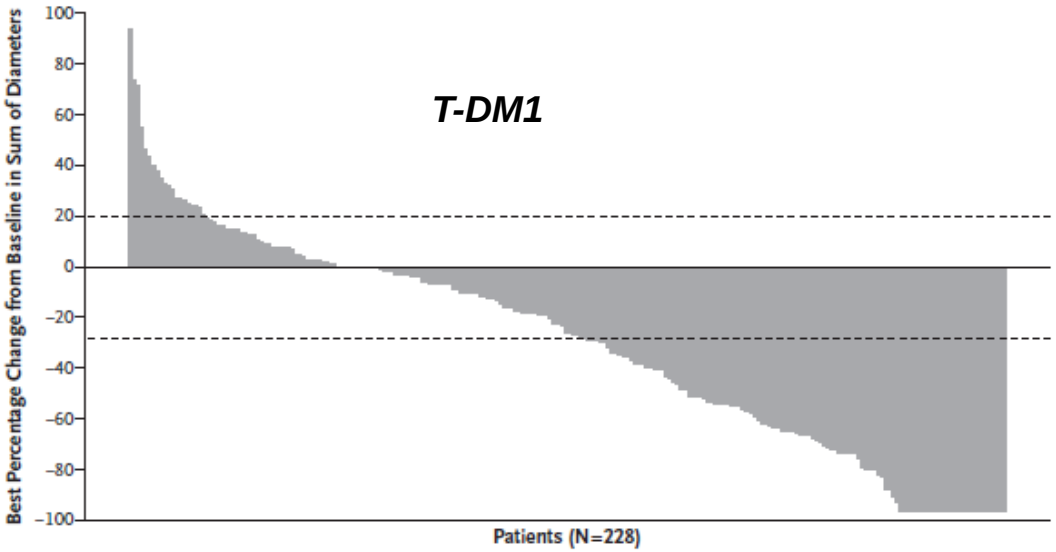
Median FU for T-DXd was 28,4 months and for T-DM1 was 26,5 months



Hurvitz SA et al., Lancet 2023

DESTINY-Breast03: ORR and best response





	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

Cortès J ESMO 2021; Cortès J et al., NEJM 2022

DESTINY-Breast03: safety (1)

TEAEs in ≥20% of patients

System Organ Class Preferred Term, n (%)	T-DXd (n = 257) Any Grade	 Grade ≥3	T-DM1 (n = 261) Any Grade	 Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	31 (11.9)	8 (3.1)
Anemia[b]	84 (32.7)	15 (5.8)	45 (17.2)	11 (4.2)
Leukopenia[c]	78 (30.4)	17 (6.6)	22 (8.4)	1 (0.4)
Thrombocytopenia[d]	66 (25.7)	18 (7.0)	139 (53.3)	65 (24.9)
Gastrointestinal disorders				
Nausea	195 (75.9)	17 (6.6)	79 (30.3)	1 (0.4)
Vomiting	126 (49.0)	4 (1.6)	26 (10.0)	1 (0.4)
Diarrhea	75 (29.2)	1 (0.4)	18 (6.9)	1 (0.4)
Constipation	88 (34.2)	0	51 (19.5)	0
General disorders				
Fatigue[e]	126 (49.0)	13 (5.1)	90 (34.5)	2 (0.8)
Headache	56 (21.8)	0	42 (16.1)	0
Investigations				
AST increased	66 (25.7)	2 (0.8)	105 (40.2)	13 (5.0)
ALT increased	56 (21.8)	4 (1.6)	77 (29.5)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	75 (29.2)	3 (1.2)	44 (16.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	95 (37.0)	1 (0.4)[f]	8 (3.1)	0

Most drug-related TEAES were gastrointestinal or hematological in nature.

Cortes J, ESMO 2021

DESTINY-Breast03: safety (2)

Adverse events of special interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all LVEF adverse events reported were asymptomatic and no cases of cardiac failure occurred

Cortes J, ESMO 2021

Guidelines for the management of T-DXd induced ILD:

Grade 1	Grade 2	Grade 3/4

• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks
• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines[a]
	• Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks
	• Monitor symptoms closely
	• Re-image as clinically indicated
	• If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  • Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)
	  • Re-consider additional work-up for alternative etiologies as described above
	  • Escalate care as clinically indicated
		• Hospitalization required.
		• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks
		• Re-image as clinically indicated
		• If still no improvement within 3 to 5 days,
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Consider other immunosuppressants and/or treat per local practice

Incidence of ILD after implementation of toxicity management guidelines:

Updated toxicity management guidelines implemented (December 2019)

Incidence of ILD over time

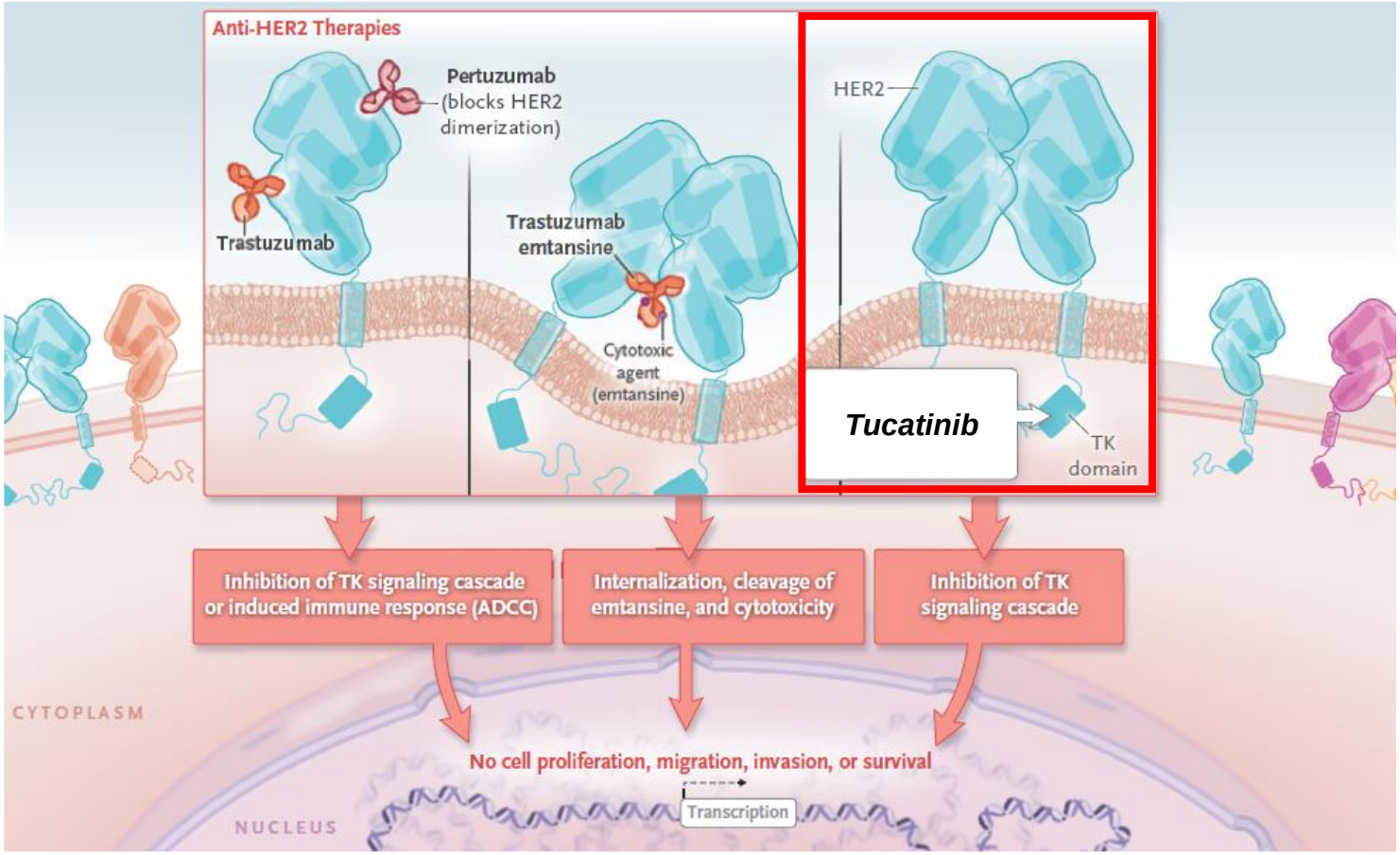
	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

- Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade ≥3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years based on a December 2020 snapshot; however, this may be partly due to the shorter treatment duration

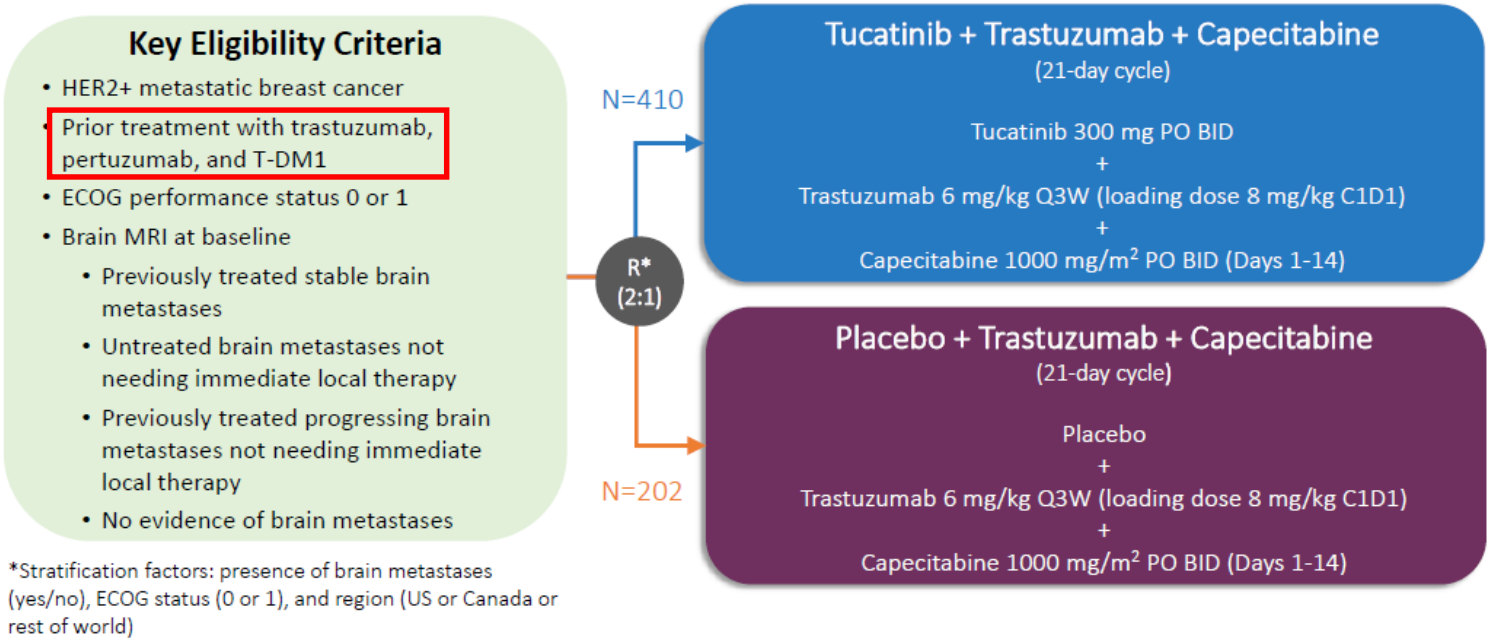
Powell C et al., AACR 2021

HER2-selective TKI: Tucatinib



Hayes DF, NEJM 2019

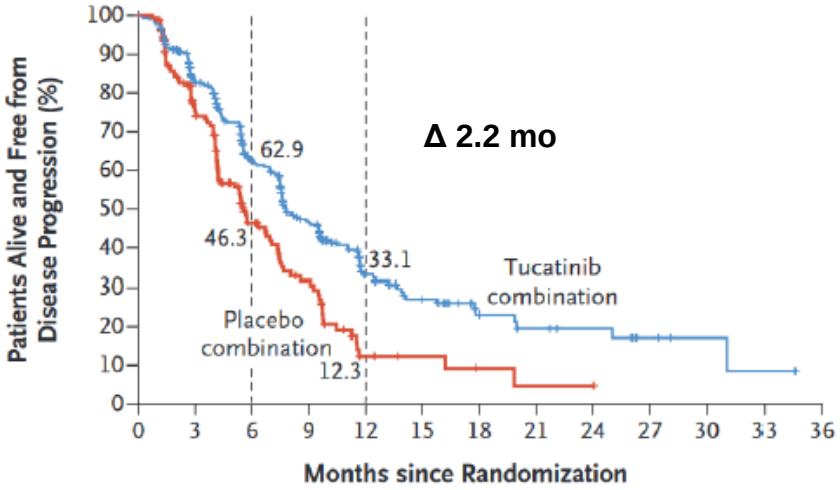
HER2CLIMB:
study design and patients' characteristics



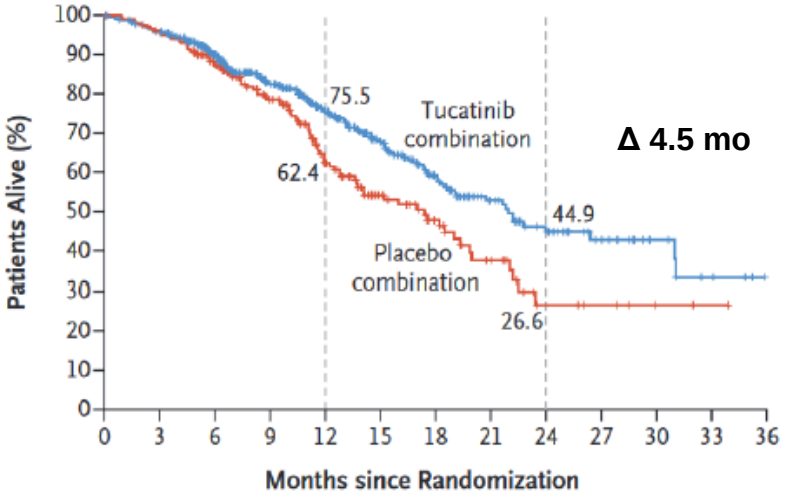
Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2,17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Presence/history of brain metastases		198 (48)	93 (46)

Murthy RK et al., NEJM 2020

HER2CLIMB: PFS and OS results



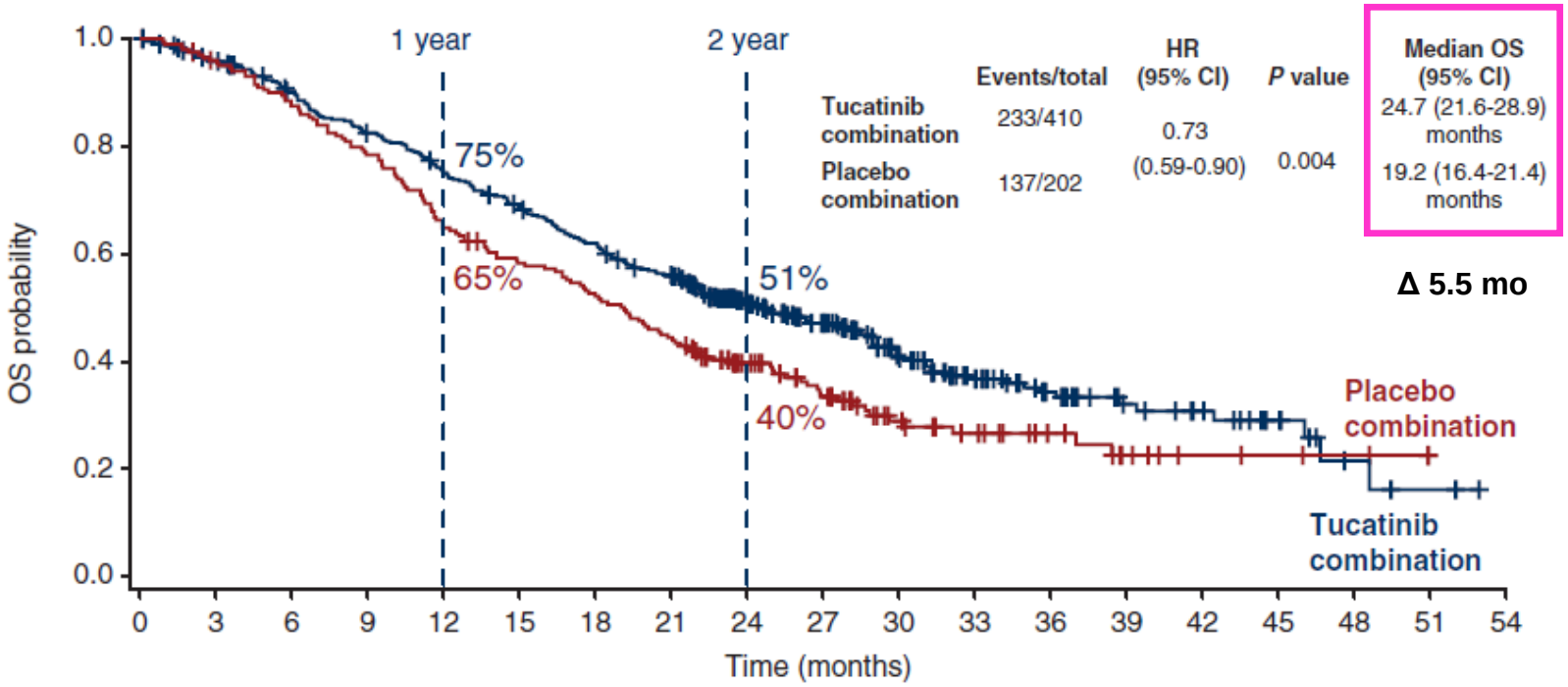
	Events/pts	mPFS	HR (95%CI
Tucatinib combination	178/320	7.8	
Placebo combination	97/160	5.6	0.54 (0.42-0.71)



	Events/pts	mOS	HR (95%CI
Tucatinib combination	130/410	21.9	
Placebo combination	85/202	17.4	0.66 (0.50-0.88)

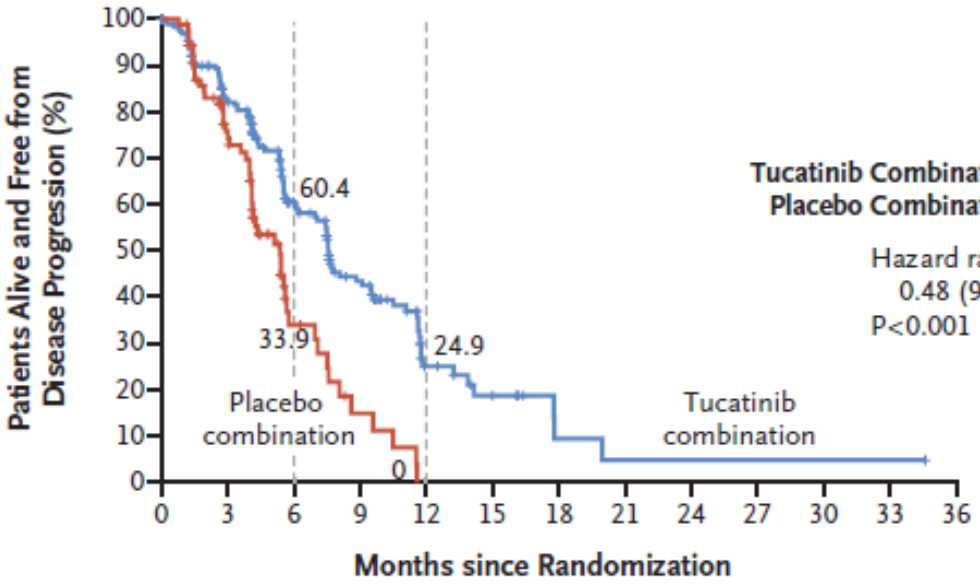
Murthy RK et al., NEJM 2020

HER2CLIMB: final OS analysis



Curigliano G et al., Annals of Oncology 2022

HER2CLIMB: PFS and ORR among patients with brain metastases



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

Δ 2.2 mo

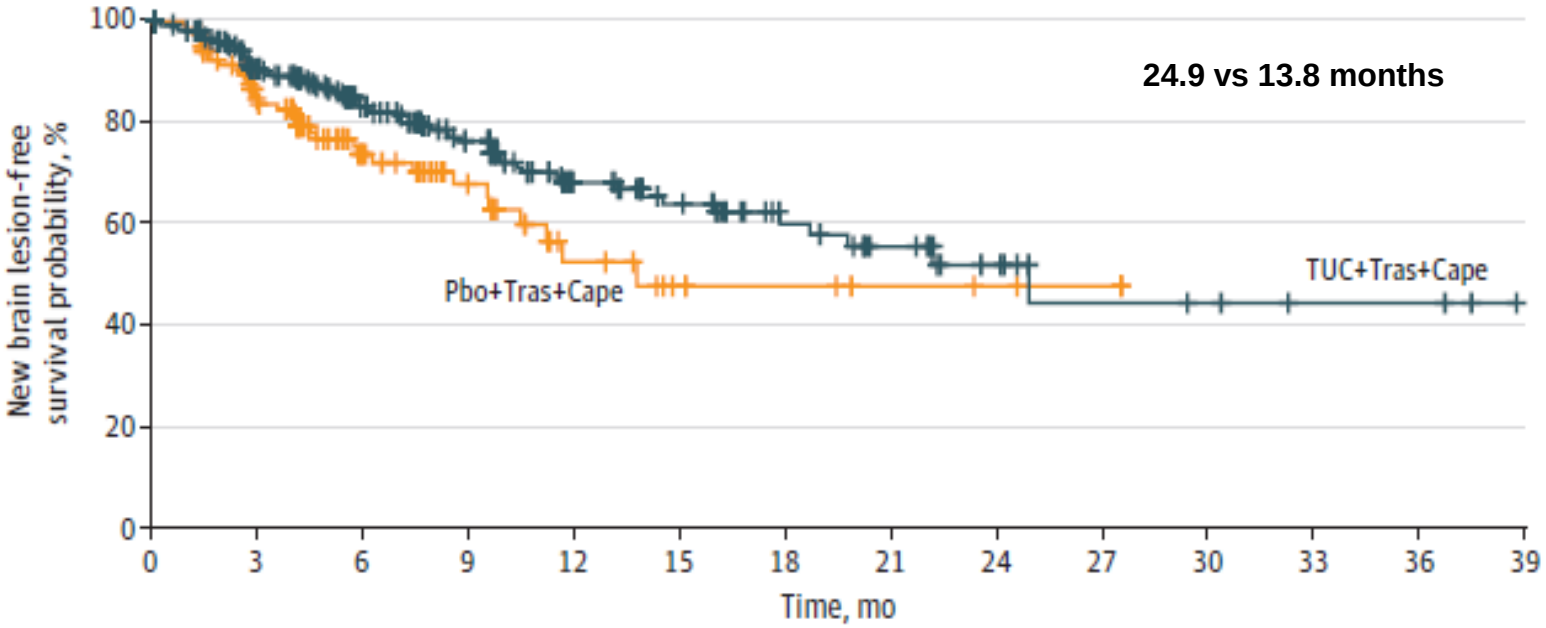
Murthy RK et al., NEJM 2020

	TUC+Tras+Cape, (N=55)	Pbo+Tras+Cape, (N=20)
Patients with Objective Response of Confirmed CR or PR, n	26	4
Confirmed ORR-IC, % (95% CI)	47.3 (33.7, 61.2)	20.0 (5.7, 43.7)
DOR-IC[a], months (95% CI)	8.6 (5.5, 10.3)	3.0 (3.0, 10.3)

More frequent and more durable intracranial responses with tucatinib

Lin et al., SABCS 2021

HER2CLIMB: new brain lesion-free survival



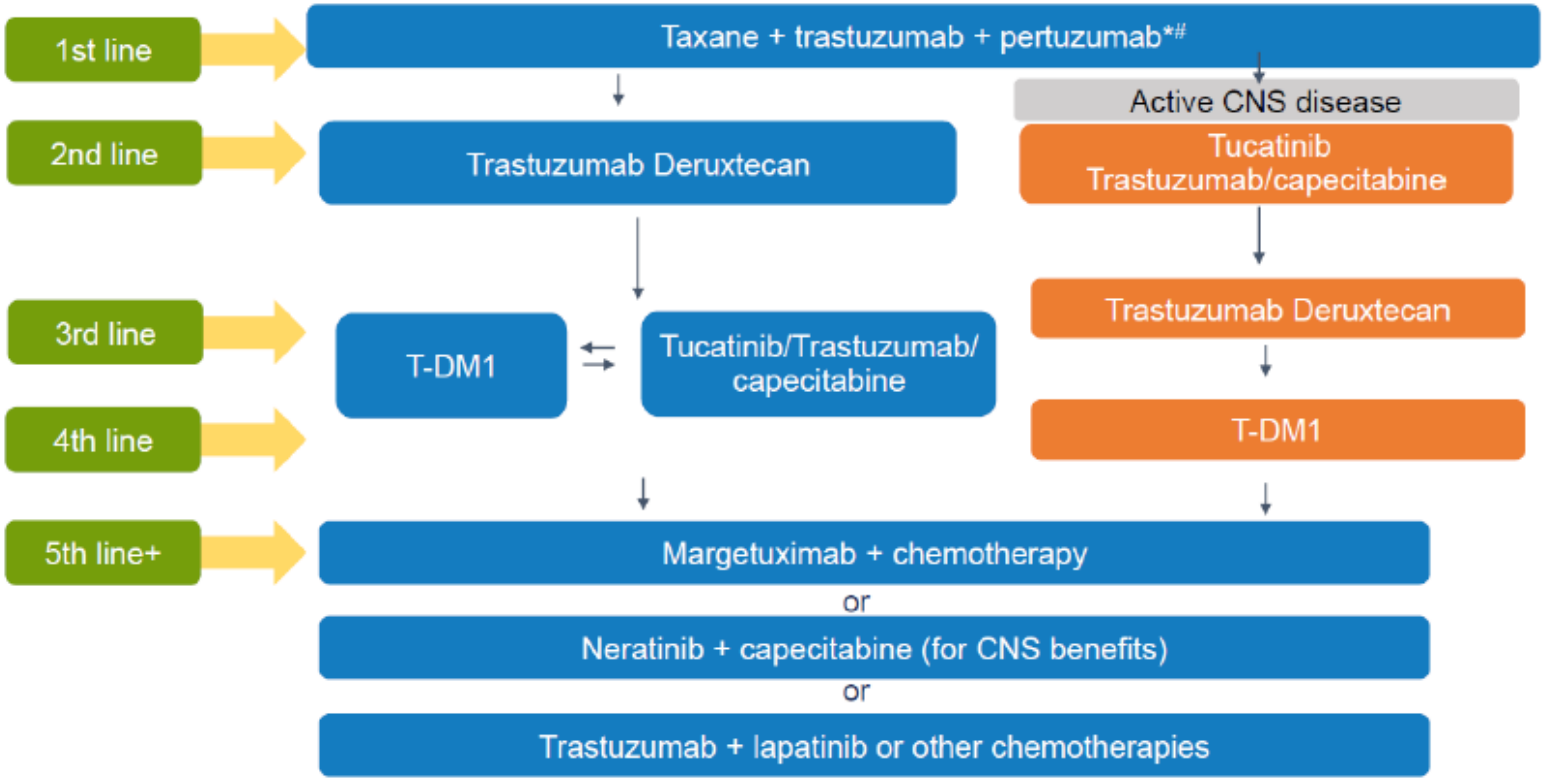
Lin NU et al., JAMA Oncol 2022

HER2CLIMB: safety

Event	Tucatinib-Combination Group (N = 404)		Placebo-Combination Group (N = 197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

Murthy RK et al., NEJM 2020

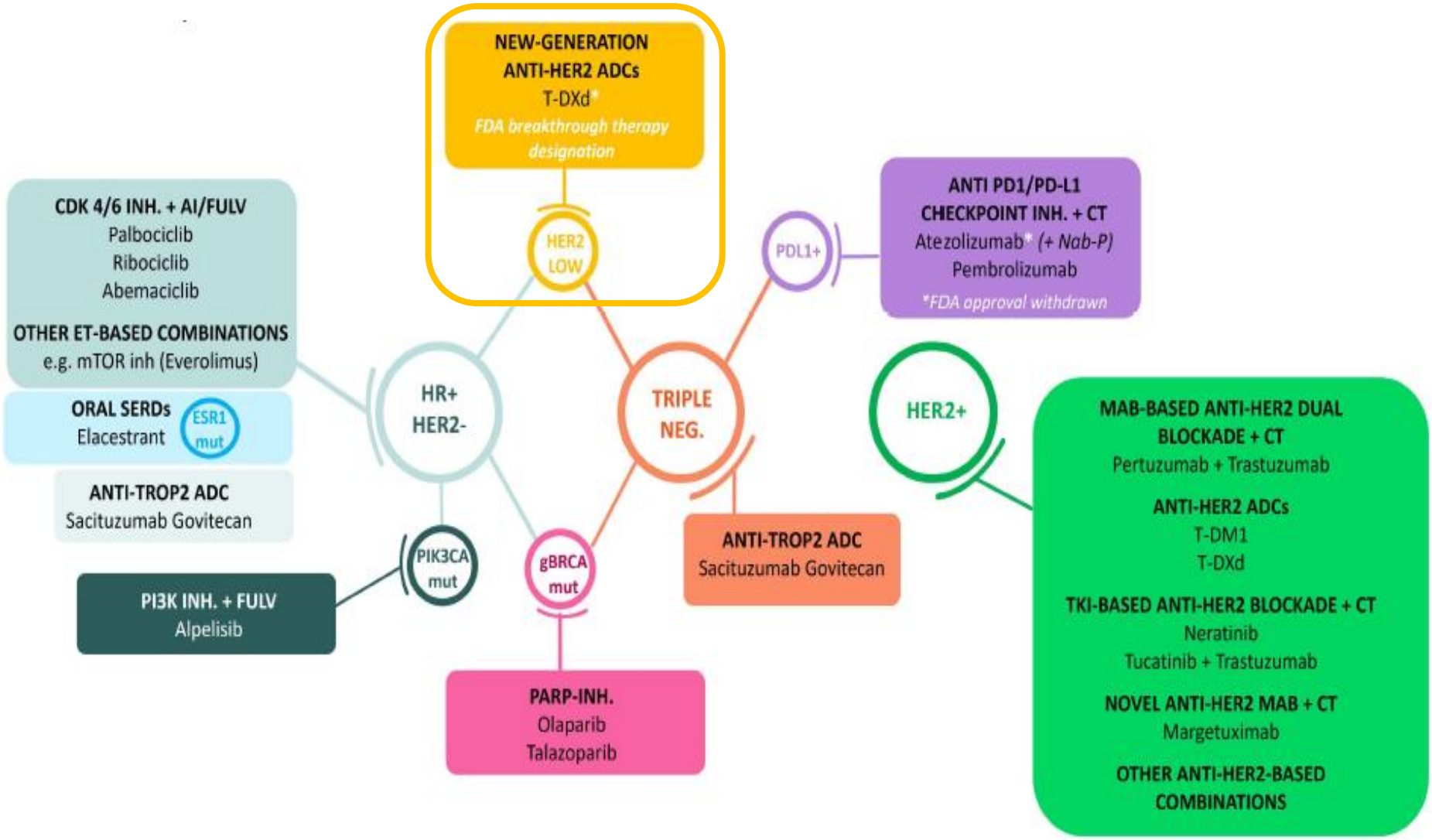
Post-ESMO 2021 treatment algorithm for HER2+ MBC



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

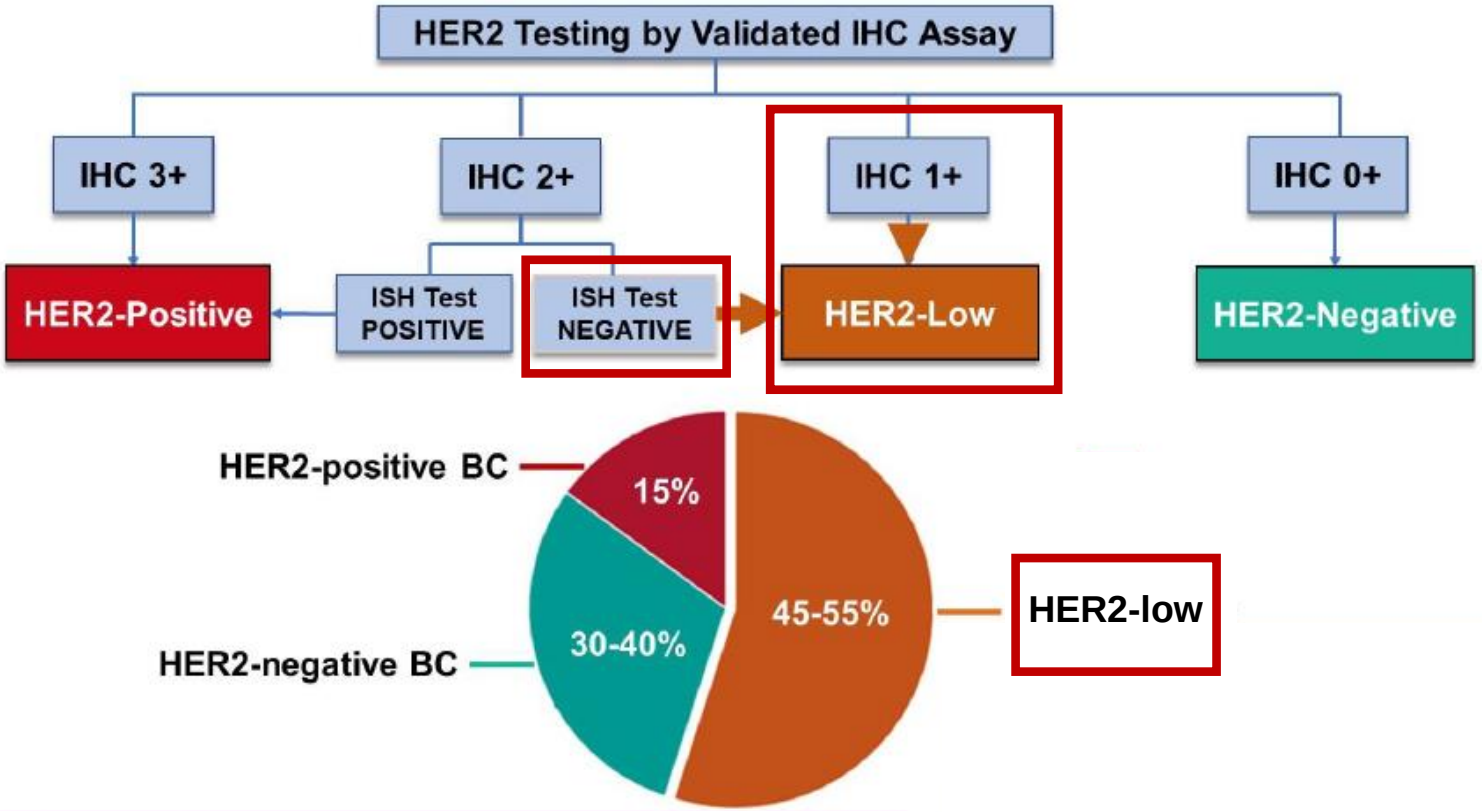
Courtesy by A Musolino

HER2-low MBC:



Miglietta F et al., ESMO Open 2022

HER2-low BC definition and features

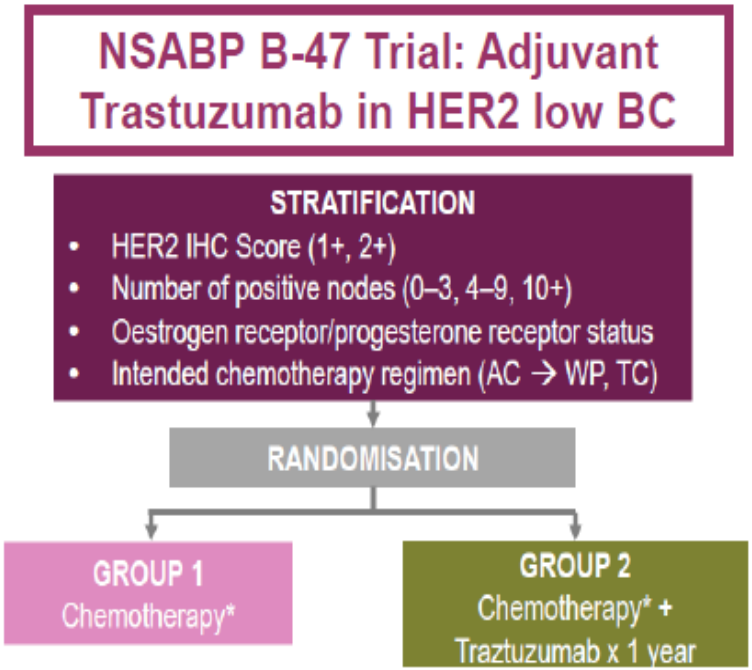


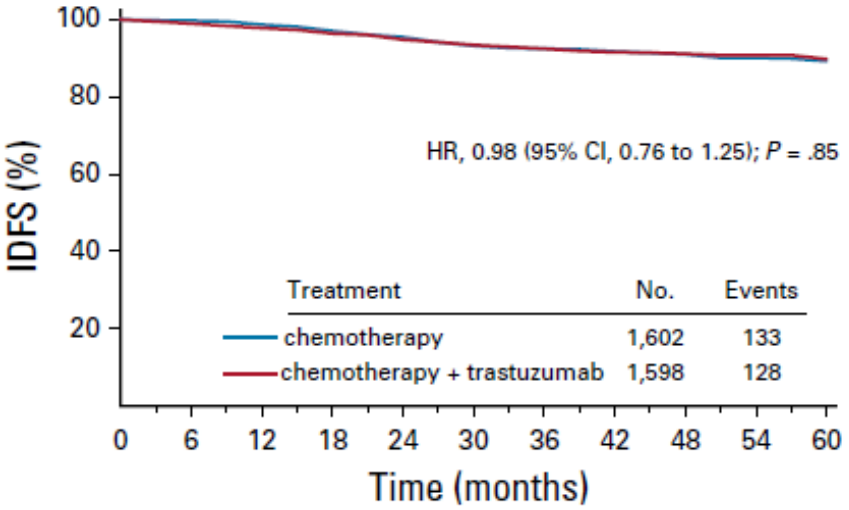
- **Most HER2-low BC expressed hormone receptors**:
  - 65-85% HR+ HER2-low
  - 35-15% HR- HER2-low

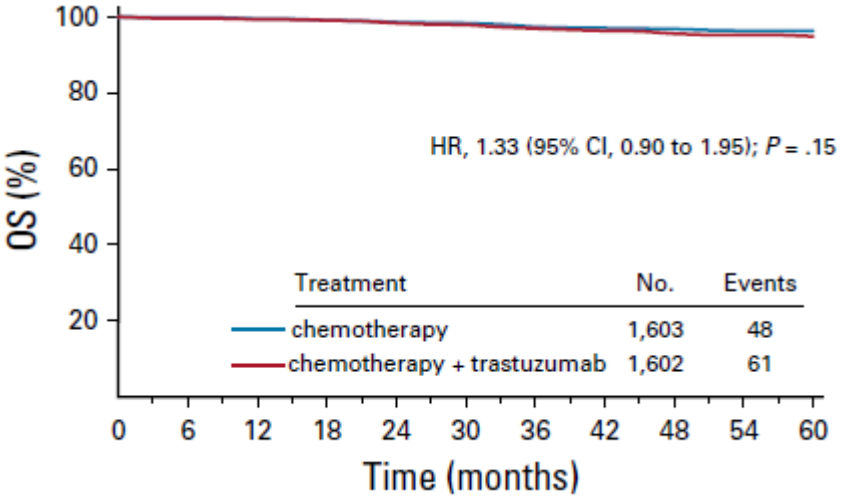
- **Similar biology and prognosis between HER2-low and HER2 0**

Tarantino P et al., JCO 2022

Negative results of monoclonal Abs and "Old" ADC in HER2-low BC



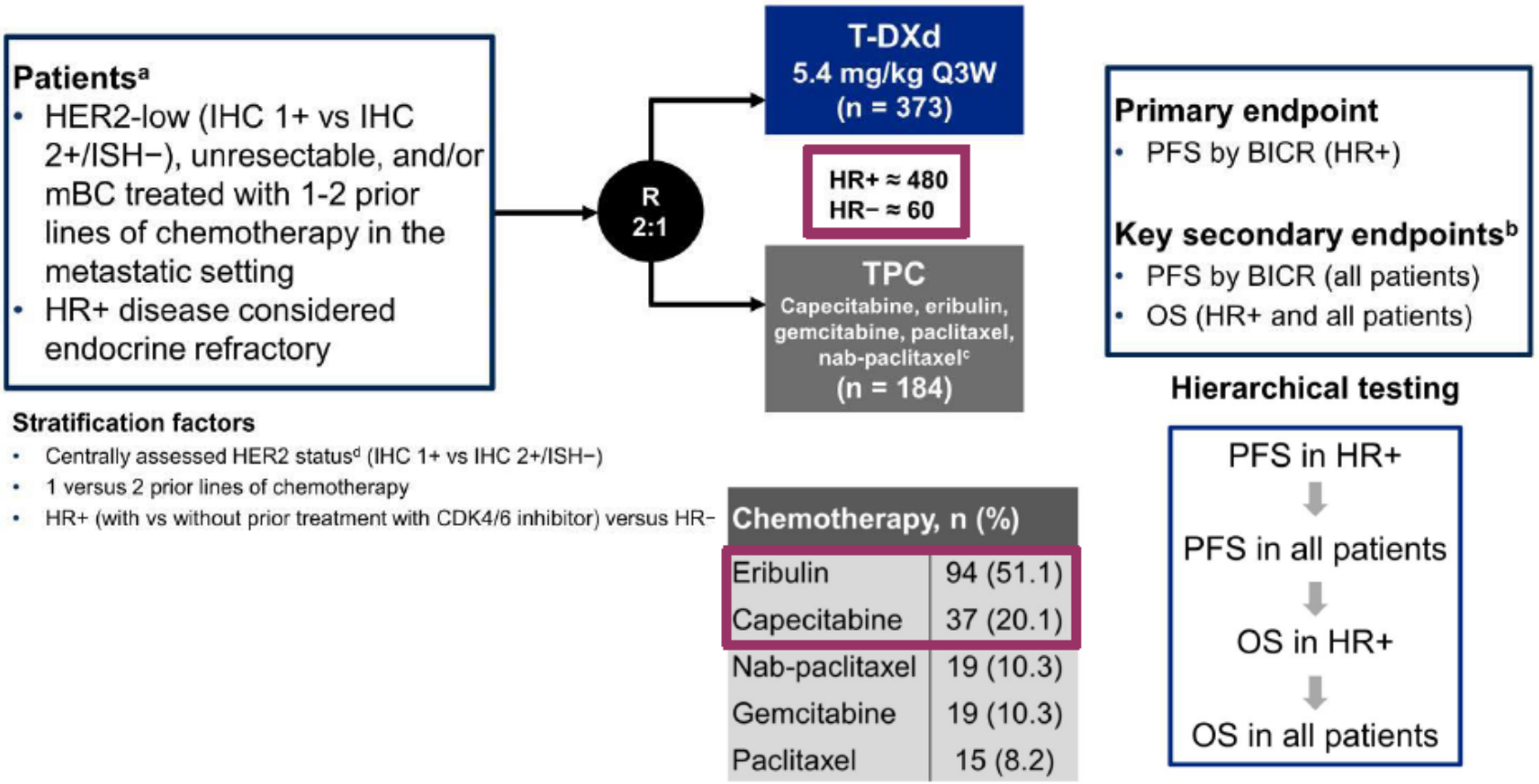




- NSABP B-47 demonstrated that adjuvant Trastuzumab is NOT effective in these tumors, likely due to their low or absent addiction to HER2 signalling.
- Similar NEGATIVE results with Pertuzumab and TDM1 in advanced setting.

Fehrenbacher L et al., JCO 2019; Gianni L et al. JCO 2010; Burris H et al., JCO 2011; Paik S et al., NEJM 2008

DESTINY-Breast04: study design



Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

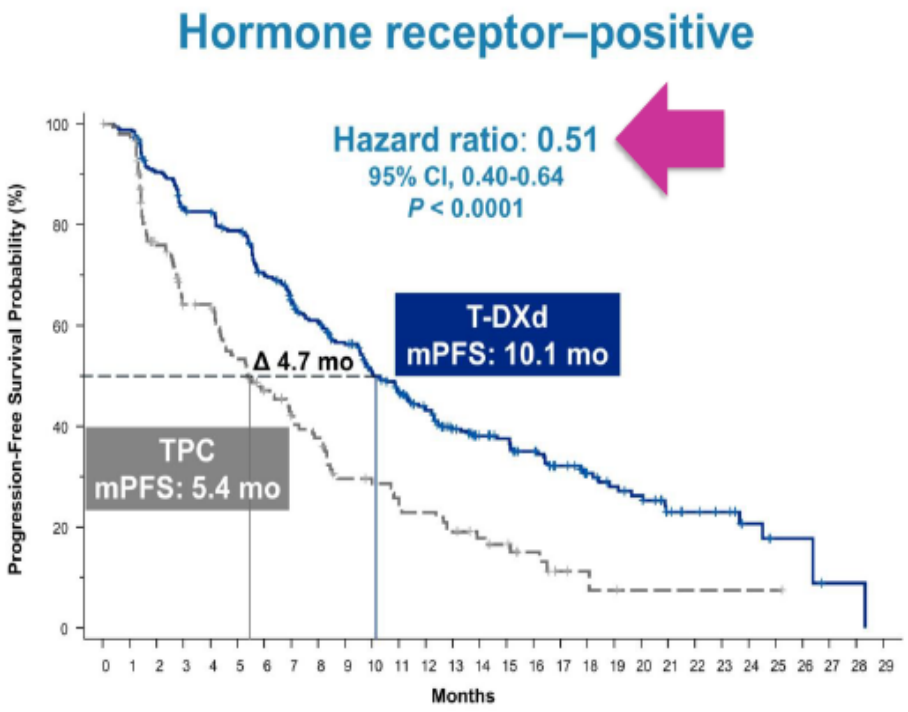
Modi S, ASCO 2022; Modi S et al., NEJM 2022

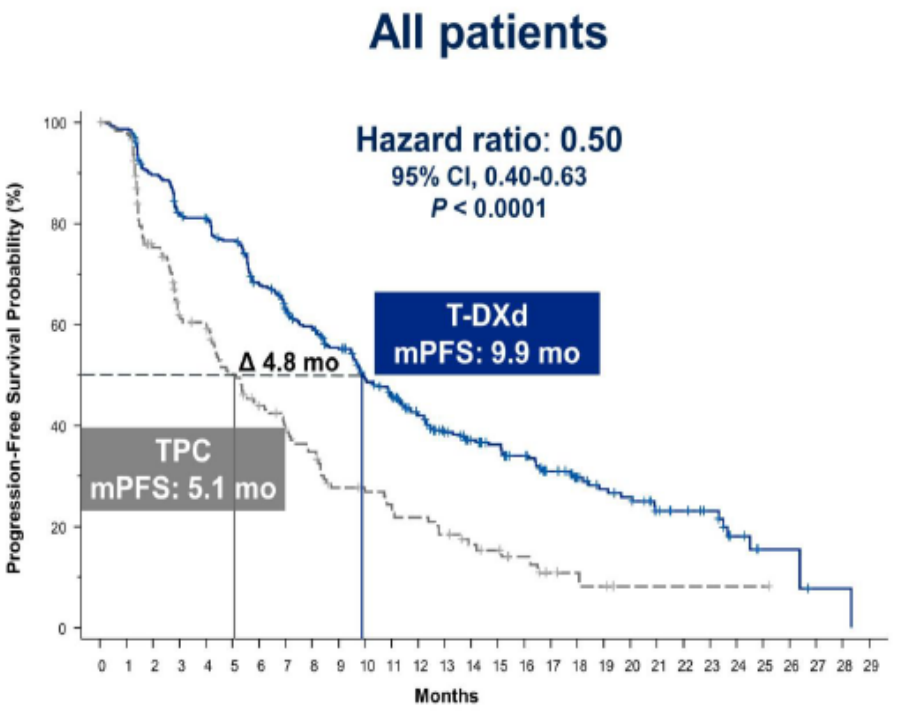
DESTINY-Breast04: patients' characteristics

Characteristic	Hormone Receptor–Positive Cohort		All Patients	
	Trastuzumab Deruxtecan (N=331)	Physician's Choice of Chemotherapy (N=163)	Trastuzumab Deruxtecan (N=373)	Physician's Choice of Chemotherapy (N=184)
Hormone receptor–positive — no. (%)¶	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Metastasis — no. (%)				
Brain	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Liver	247 (74.6)	116 (71.2)	266 (71.3)	123 (66.8)
Lung	98 (29.6)	58 (35.6)	120 (32.2)	63 (34.2)
Previous cancer therapy — no. (%)				
Targeted therapy	259 (78.2)	132 (81.0)	279 (74.8)	140 (76.1)
CDK4/6 inhibitor	233 (70.4)	115 (70.6)	239 (64.1)	119 (64.7)
Immunotherapy	10 (3.0)	8 (4.9)	20 (5.4)	12 (6.5)
Other	128 (38.7)	70 (42.9)	140 (37.5)	76 (41.3)
Endocrine therapy	330 (99.7)	160 (98.2)	347 (93.0)	165 (89.7)
Chemotherapy	331 (100)	162 (99.4)	373 (100)	183 (99.5)
Lines of therapy for metastatic disease				
Median no. of lines (range)	3 (1–9)	3 (1–8)	3 (1–9)	3 (1–8)
No. of lines — no. of patients (%)				
1	23 (6.9)	14 (8.6)	39 (10.5)	19 (10.3)
2	85 (25.7)	41 (25.2)	100 (26.8)	53 (28.8)
≥3	223 (67.4)	108 (66.3)	234 (62.7)	112 (60.9)

Modi S et al., NEJM 2022

DESTINY-Breast04: PFS



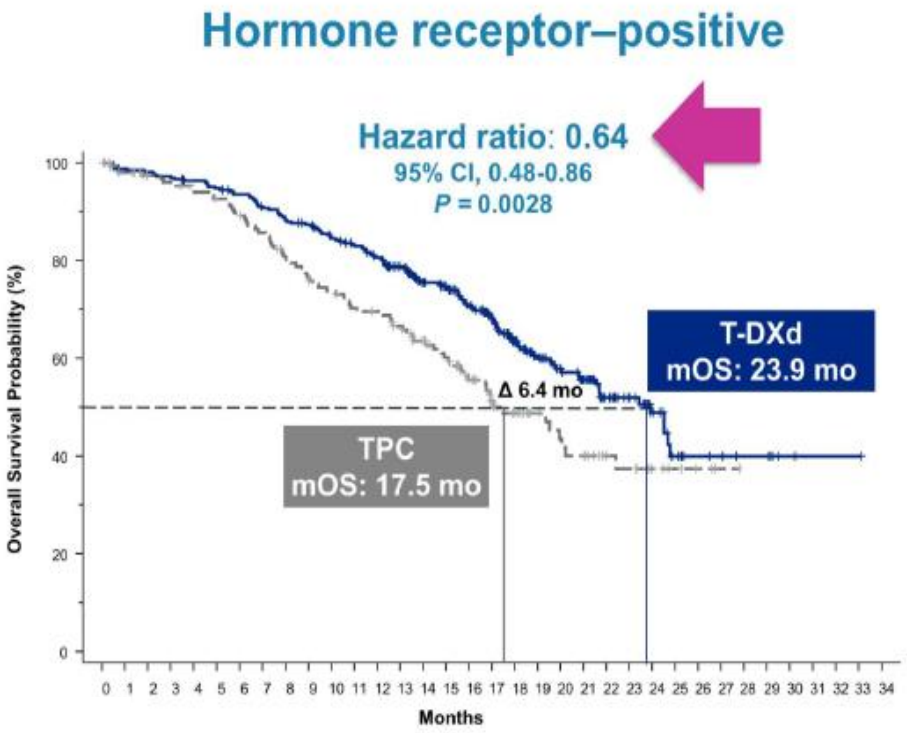


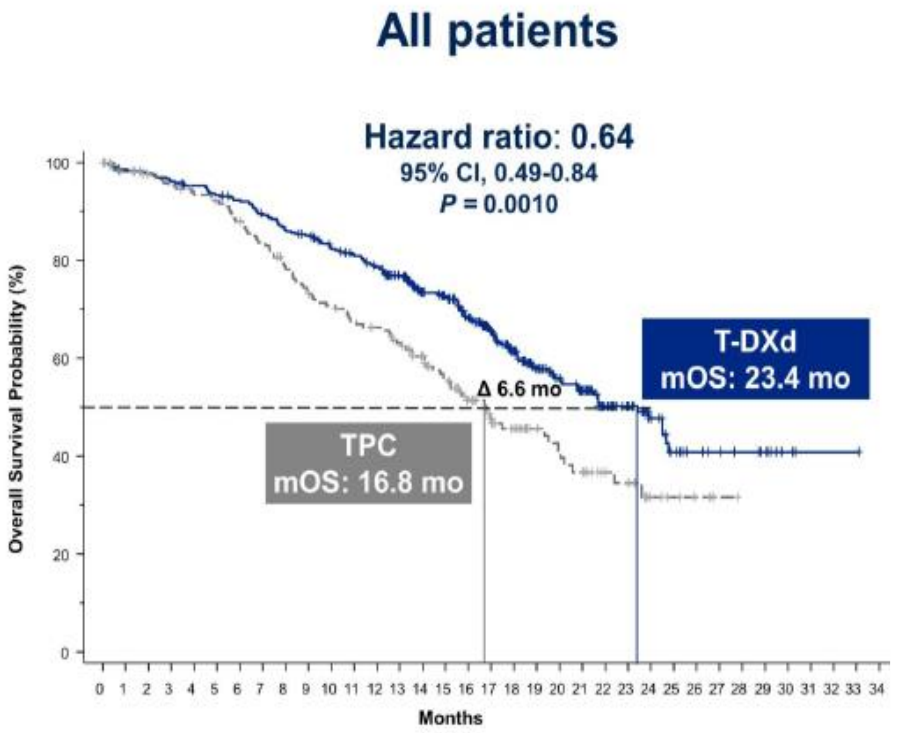
median FU: 18.4 months

Benefit was observed across all stratification subgroups, including according to HER2-low (IHC1+ or IHC2+IISH-) and prior CDK4/6i

Modi S et al., NEJM 2022

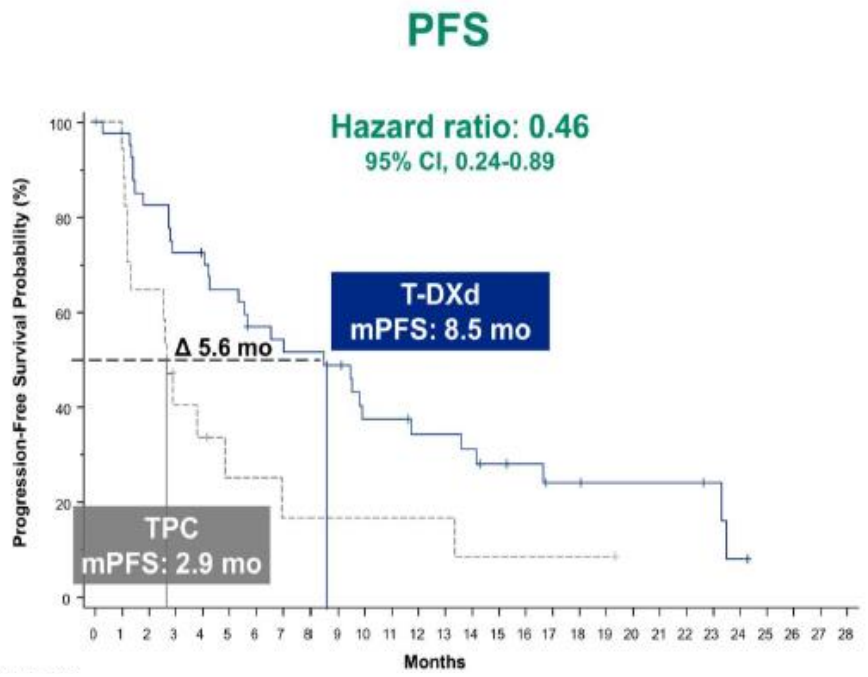
DESTINY-Breast04: OS

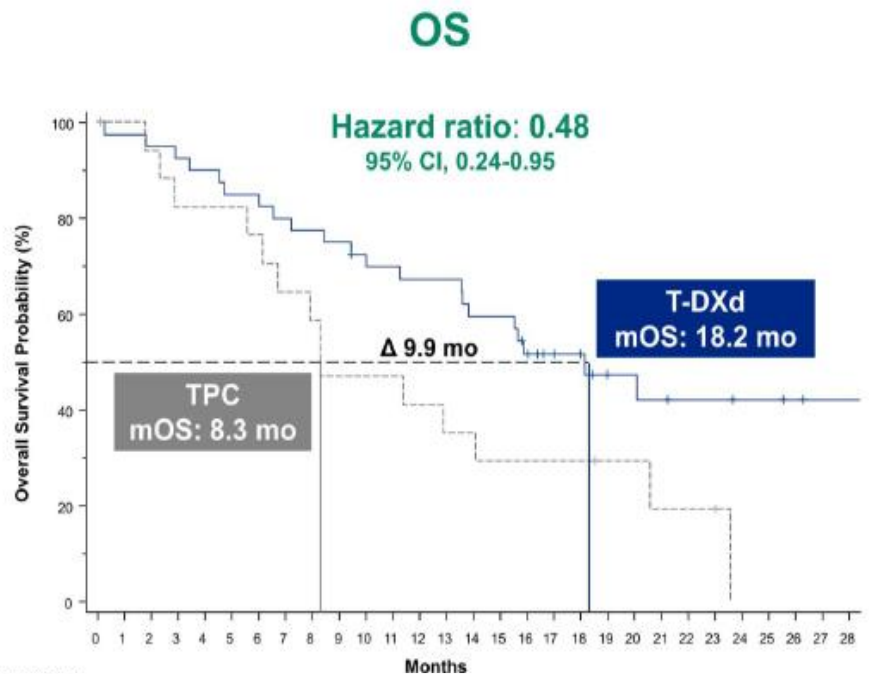




Modi S et al., NEJM 2022

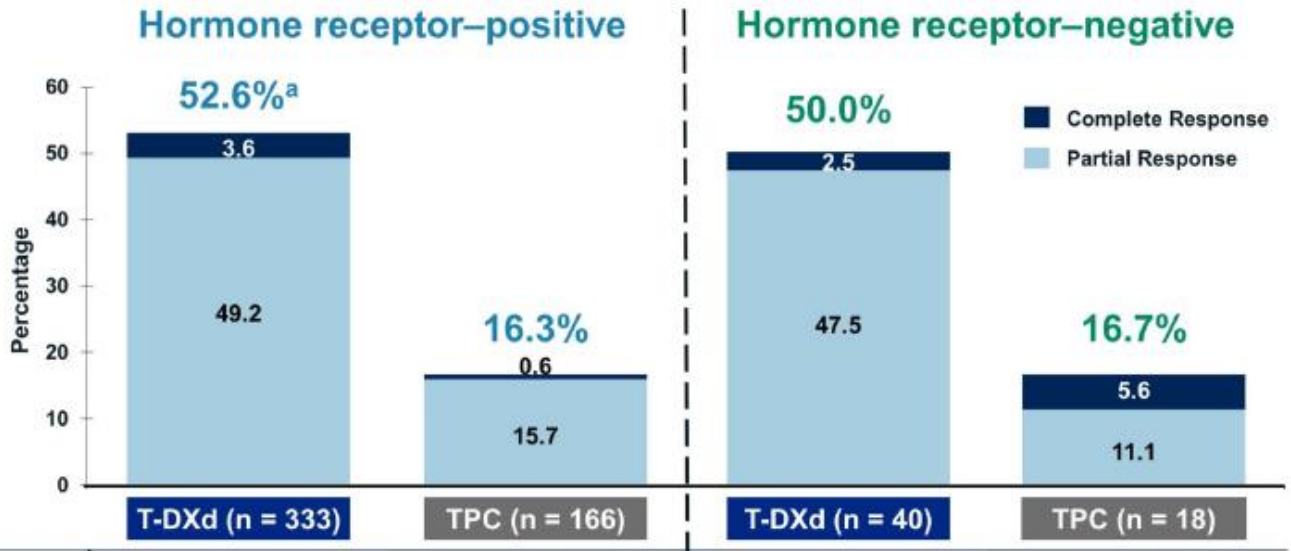
DESTINY-Breast04: similar results in HR- (Exploratory analysis)





Modi S et al., NEJM 2022

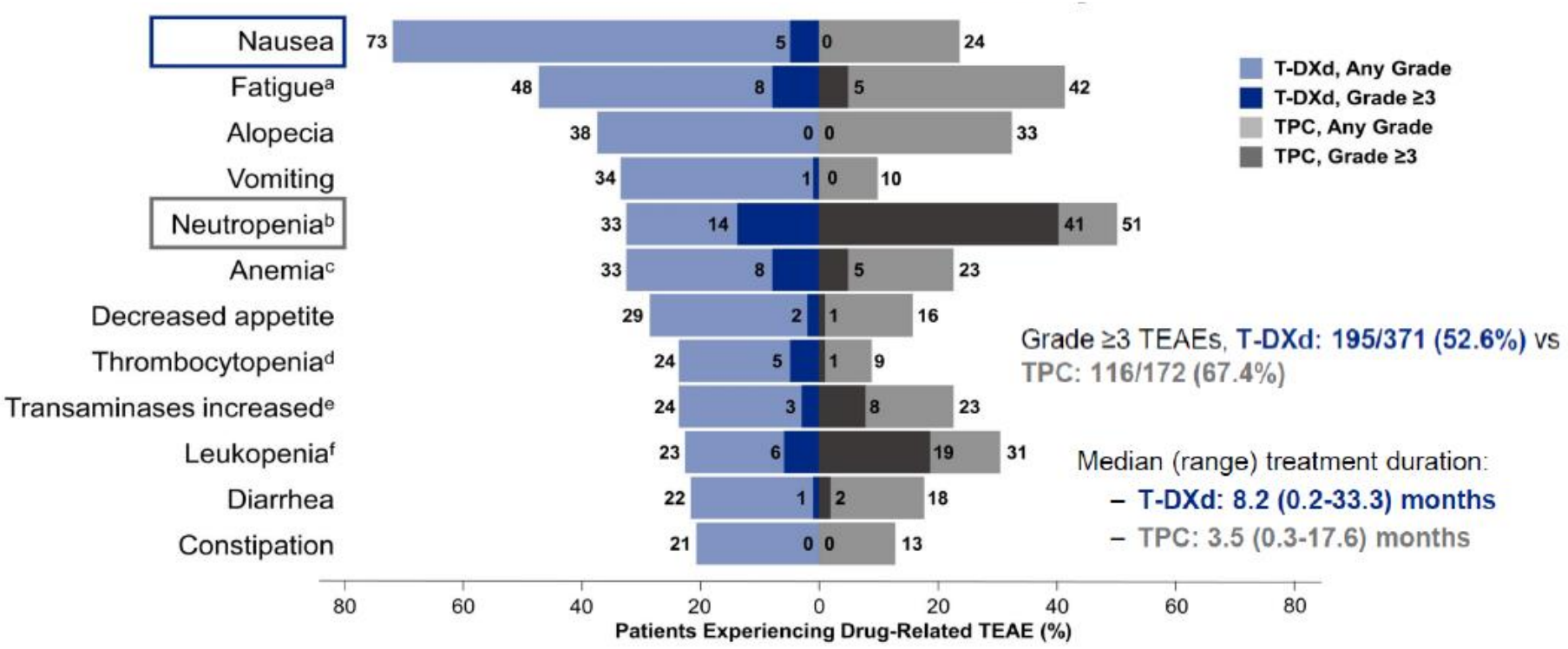
DESTINY-Breast04: ORR, CBR and duration of response



Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Modi S et al., NEJM 2022

DESTINY-Breast04: safety

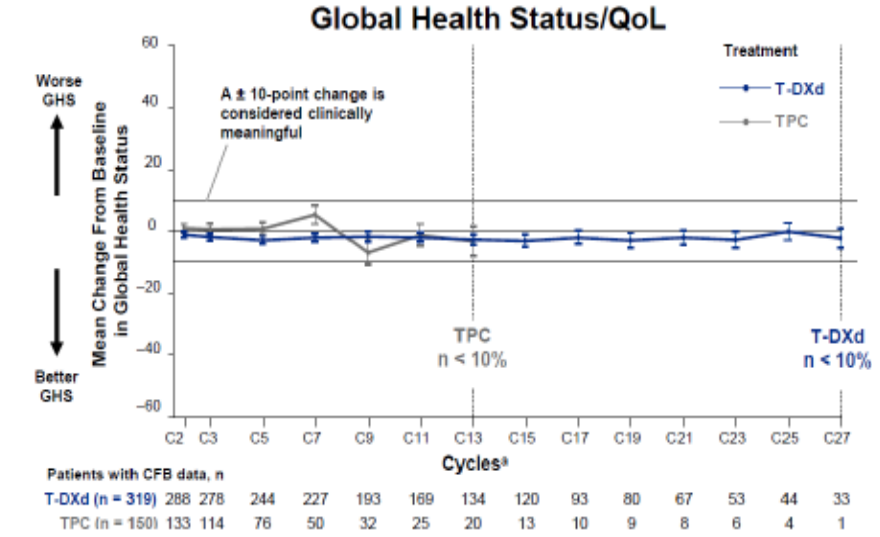


Adjudicated as drug-related ILD/pneumonitis[a]

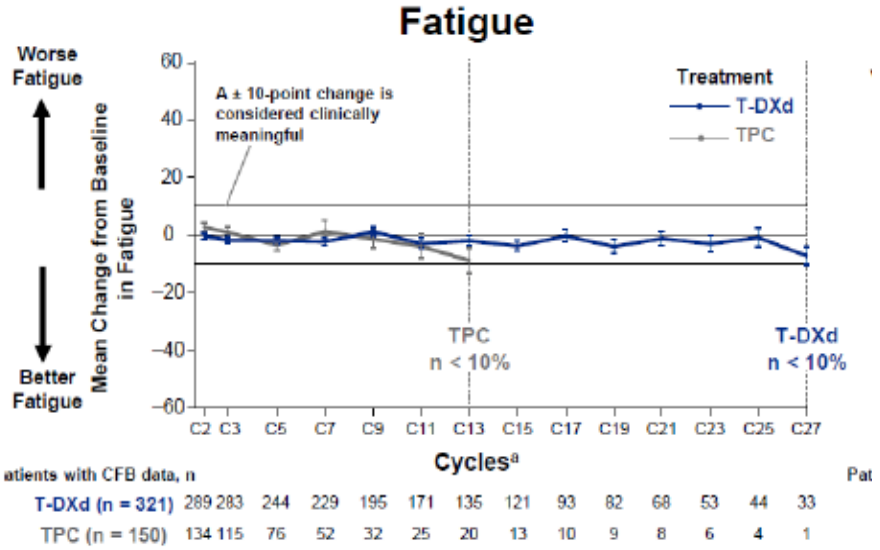
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

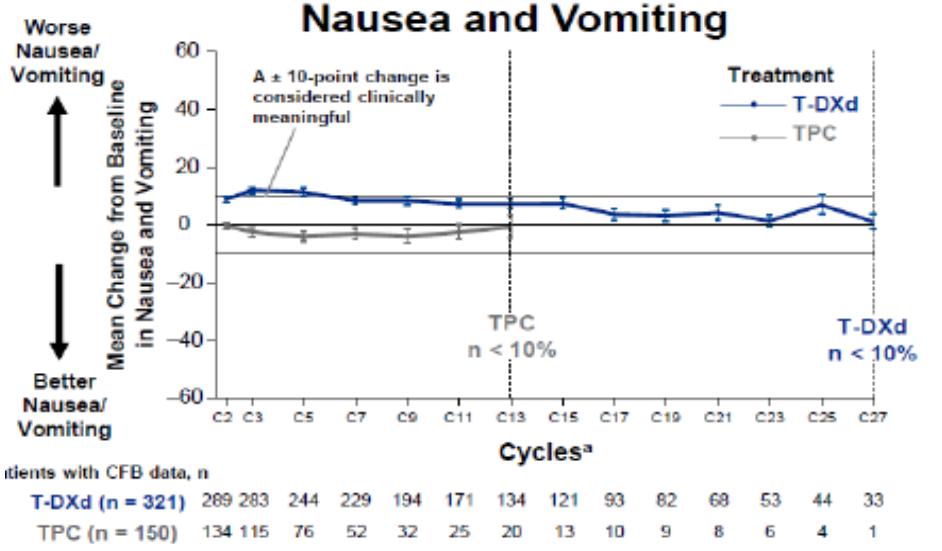
Modi S et al., NEJM 2022

DESTINY-Breast04: PROs (1)



- GHS/QoL was maintained with T-Dxd and TPC (QLQ-C30).
- Fatigue scores remained stable over time in both treatment arms.
- **With T-DXd, an increase in nausea and vomiting scores was only clinically relevant in early cycles,** after which scores decreased and remained stable over time.

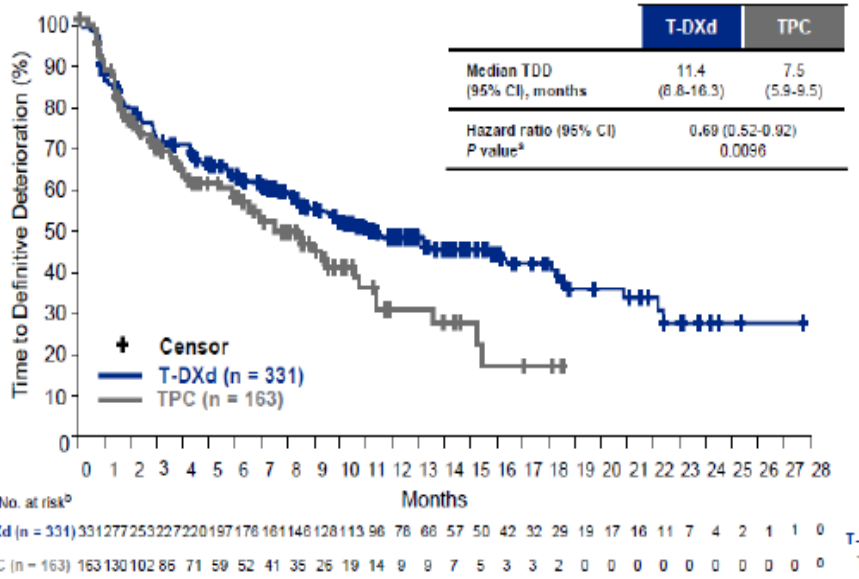




Naoto T Ueno et al, ESMO 2022

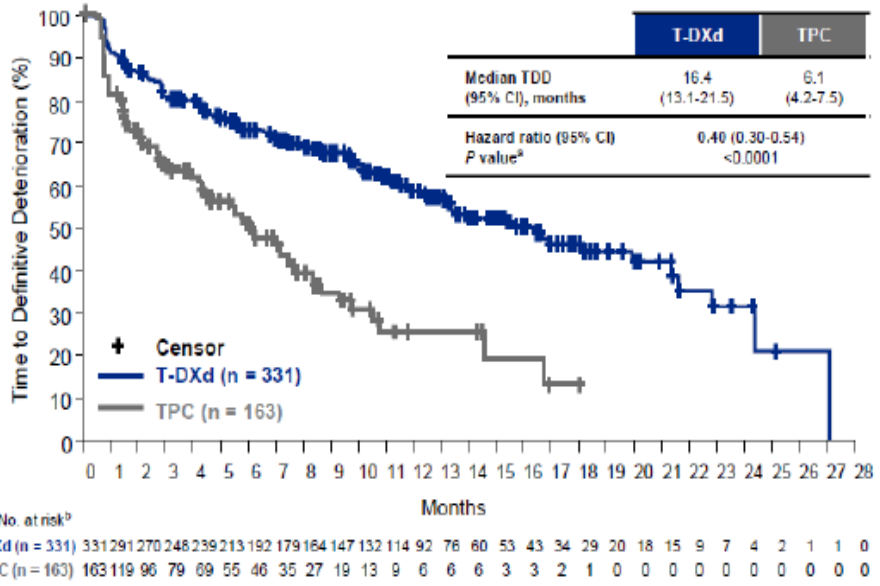
DESTINY-Breast04: PROs (2)

GHS/QoL



	T-DXd	TPC
Median TDD (95% CI), months	11.4 (8.8-16.3)	7.5 (5.9-9.5)
Hazard ratio (95% CI)	0.69 (0.52-0.92)	
P value[a]	0.0096	

Pain Symptoms



	T-DXd	TPC
Median TDD (95% CI), months	16.4 (13.1-21.5)	6.1 (4.2-7.5)
Hazard ratio (95% CI)	0.40 (0.30-0.54)	
P value[a]	<0.0001	

- **Time to definitive deterioration of GHS/QoL and pain was longer among patients who received T-DXd vs TPC (QLQ-C30)**
- T-DXd treatment delays the deterioration of GHS/QoL and shows a QoL benefit of T-DXd vs TPC in patients with HR+/HER2-low mBC

Naoto T Ueno et al, ESMO 2022

Conclusions:

- HER2-low BC is defined by IHC score 1+ or 2+/ISH-
  - Nearly 50% of all BC are HER2-low
  - HER2-low are more common among Luminal-Like tumors than TNBC
  - HER2-low seems to have no distinct biology/prognosis than HER2 score 0
- Negative results in HER2-low with '*Old*' anti-HER2 Abs and ADCs
- HER2-low BC emerges as a new druggable entity, through the delivery of payloads
- Destiny-Breast04 established T-Dxd as a new standard of care in HER2-low BC

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